IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Examiner: Michele C. Flood
Christopher O. Okunji, et al.	Group Art Unit: 1655
Serial No.: 09/428,203	
Filing Date: October 27, 1999	
For: PLANT DERIVED ANTI-PARASITIC AND ANTI-FUNGAL COMPOUNDS AND METHODS OF EXTRACTING THE COMPOUNDS	

APPEAL BRIEF

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants submit the following Appeal Brief. This brief is timely filed within the two month period of response that expires on May 24, 2009. The Commissioner is hereby authorized to charge any fees that are required, as well as any additional fees that may be required in connection with the filing of this paper, or credit any overpayment, to U.S. Army Medical Research and Materiel Command, Deposit Account Number 210380. Please send all correspondence to Ms. Elizabeth Arwine, Esq.; Office of the Staff Judge Advocate; U.S. Army Medical Research and Materiel Command; 504 Scott Street; Fort Detrick, MD 21702-5012; Attn: MCMR-JA (Ms. Arwine). Please direct any questions regarding this case to Ms. Abanti (Abby) Bhattacharyya, Esq., at (410) 964-9553.

05/27/2009 NNGUYEN1 00000006 210380 09428203
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Sincerely,

May 22, 2009
Date

Abanti A Bhattacharyya, Esq.
Reg. No. 36,681

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	Examiner: Michele C. Flood
Christopher O. Okunji, et al.	)	Group Art Unit: 1655
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APPEAL BRIEF

TABLE OF CONTENTS

I. REAL PARTY IN INTEREST

The real party in interest is the United States Army, as represented by the U.S. Army Medical Research and Materiel Command of Fort Detrick, Maryland.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences that will affect or be affected by the outcome of this appeal.

III. STATUS OF THE CLAIMS

For the purposes of this Appeal, Applicants provide a status of the claims that conforms with the non-entered amendment of July 24, 2008. Thus, the present application recites claims 1 through 40. Claim 1 is currently pending in this application. Claims 2 through 10 are cancelled. Claim 11 is currently pending in this application. Claims 12 through 29 are cancelled. Claim 30 is currently pending in this application. Claims 31 through 37 are cancelled. Claim 38 is currently pending in this application. Claims 39 through 40 are cancelled.

IV. STATUS OF THE AMENDMENTS

An amendment and response was filed by Applicants on July 24, 2008, in response to the Examiner's final rejection of March 28, 2008. The amendment and response was not entered. For the purposes of this Appeal, Applicants respectfully request that only the claims of the non-entered amendment, claims 1, 11, 30 and 38, be considered.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Claim 1 is directed to a saponin-enriched fractionated extract of *Napoleonaea imperialis* that exhibits anti-leishmanial activity. The extract has been effective in treating *Leishmania* while having low-toxicity for humans. *See* Specification at 14. The recitation in claim 1 is based upon findings that traditional medicines may provide efficacy against protozoan infections without the side-effects encountered when utilizing conventional pharmaceuticals. Claim 11 is dependent upon claim 1 and recites direct solvent extraction of the powdered seeds of *Napoleonaea imperialis*. Direct solvent extraction of the powdered seeds was found to be the most effective technique to extract the saponin-enriched fraction recited in claim 1. *See id.* The extraction was conducted in three batches utilizing the solvents hexane, chloroform, ethyl acetate and methanol. The methanol extract was found to be the most active fraction and is recited in claim 30, which is dependant upon claim 1, and claim 38, which is dependant upon claim 11.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds of rejection to be reviewed in this appeal are as follows:

A. Are claims 1, 11, 30 and 38 unpatentable under 35 U.S.C. 112 2nd paragraph for failing to particularly point out and distinctly claim the subject matter by reciting "A biologically active extract comprising a fractionation extract." Additionally, is an acknowledgement of utility by the Examiner of the term under 35 U.S.C. 101 inconsistent with a finding of ambiguity of the same term under 35 U.S.C. 112 2nd paragraph.

B. Is the Examiner's denial of entry of Applicants' Amendment and Response of July 24, 2008, outside the scope of examination practice under 37 C.F.R. 1.116(b), where Applicants have shown good and sufficient reasons for the amendments, when:

1. The Examiner's position that the grounds for non-entry of Applicants' amendment is a prior art search necessitated by amendment, based on the Applicants' claim recitation of "fractionated," where previous claims recited "fractionation;" *See* Examiner's Advisory Action at 2 (Aug. 21, 2008); *See also* Examiner's Advisory Action at 2 (Oct. 10, 2008);

2. The term "fractionated" was suggested by the Examiner in the Office Action to which the Applicants were responding; and

3. In preparing the Amendment and Response, Applicants relied on the Examiner's Office Action and subsequent telephone interview record of July 24, 2008, stating "Applicant's representative, Abby Bhattacharyya, proposes limiting the species recited in Claim 1 to *Napoleonaea imperialis* and cancelling claims 2-10, 12-29, and 31-35. Amending the claims as discussed would appear to obviate the rejections of record and place Claims 1, 11, 30 and 38 in condition for allowance absent discovery of prior art that reads on the claimed subject matter;" *See* Examiner's Office Action at 2 (Mar. 28, 2008).

C. Are claims 1, 11, 30 and 38 unpatentable under 35 U.S.C. 102(b) as being anticipated by Christopher O. Okunji, et al., *Biological Activity of Saponins from Two Dracaena Species*, 404 Adv. Exper. Med. Bio. 415 (1996).

VII. ARGUMENT

Errors of Law and Fact

1. The Examiner has made final her rejection of claims 1, 11, 30, and 38 under 35 U.S.C. 112 2nd paragraph for the recitation of "a biologically active extract comprising a fractionation extract" because "it is not clear as to the subject matter to which Applicant intends to seek patent protection. For example, plant material may be initially extracted with either water or methanol as a solvent in the making of a crude plant extract followed by subjecting the crude plant extract to fractionation with one or more solvents of increasing polarity or increasing strength." *See* Office Action, at 3 (Mar. 28, 2008). The claims are argued together.

It is established that the words of the claims, asserted and unasserted, define the scope of the patented invention. *See Bell Communications Research, Inc. v. Vitalink Communications Corp.*, 55 F.3d 615, 620, 34 USPQ 2d 1816, 1819 (Fed. Cir. 1995). Despite the fact that claims are generally given their ordinary and customary meaning, patentee may choose terminology that is outside of the ordinary and customary meaning, provided that the chosen terminology is clearly defined in the Applicants' specification. *See Hoechst Celanese Corp. v. BP Chems. Ltd.*, 78 F.3d 1575, 1578, 38 USPQ2d 1126, 1129 (Fed. Circ. 1996) (holding that a technical term in patent documents is considered as having the meaning given by persons experienced in the field of the intention unless it is clear from the patent and the prosecution history that the inventor used the term with a different meaning).

Applicants contend that they are consistent with established case law and provide adequate support in the specification for the claim recited term "biologically active extract." While the term "fractionation" may have a different meaning for persons experienced in the field, the Applicants have adequately defined their meaning in the specification. Note that the

Applicants utilize "bulk extracts," "active extracts" and "fractions" interchangeably and provide substantive disclosure of the term and what is meant by it to preclude confusion by one of ordinary skill in the art. *See* Specification at 10, 15, 17. Additionally, Applicants have provided an affidavit under 37 CFR 1.132 to distinguish between "hydrolyzed extracts" and "active extracts." *See* Response (132 Declaration) at 14 (Dec. 20, 2006). Thus, it is the Applicants' position that the Examiner is factually and legally in error that Applicants' consistent recitation of "biologically active extract" is inadequately disclosed such that its meaning is ambiguous under 35 USC 112 2nd paragraph, and that the recitation renders the claims as indefinite.

In conforming with examination practices under MPEP §2107.03, the Examiner acknowledges "that Applicant has demonstrated *in vitro* and/or *in vivo* antileishmanial, antifungal or antimalarial activities of compounds AD-1 obtained from a seed extract of *Napoleonaea imperialis*, using either ethyl acetate or methanol." *See* Office Action at 3 (Apr. 4, 2002). Inherent in the Examiner's statements that Applicants conform to the *in vitro* and *in vivo* antileishmanial activity of the seed extract of *Napoleonaea imperialis* is an implicit understanding that the terminology utilized by the Applicants in the specification, the manner of its use in the specification and the conclusions reached by the Applicants is unambiguous. Without the implicit understanding, the Examiner cannot ascertain utility. Thus, if the Examiner asserts that "biologically active extracts" and "fractionation" merits substantive clarity in the specification, she cannot then assert that these terms are ambiguous in the claims, for claims must be "given the broadest reasonable interpretation consistent with the specification." *See* MPEP §904.01, §2111 (Jul 2008).

2. As provided for in 37 C.F.R 116(b), an amendment after final rejection will be entered if "(1) canceling claims or complying with any requirement of form expressly set forth in

a previous Office Action; or (3) An amendment touching the merits of the application may be admitted upon a showing of good and sufficient reason why the amendment is necessary and was not earlier presented." See 37 C.F.R. 116(b) at 89 (Jul 2008). The claims are argued together.

As stated, the Applicants' after-final Amendment of July 24, 2008, conformed to the substantive issues raised by the Examiner's Office Action of March 28, 2008. With respect to the Examiner's rejection of the claims under 35 U.S.C. 112 2nd paragraph, Applicants provided amendments to limit claim recitation to a fractionated seed extract of *Napoleonaea imperialis* and the solvent methanol. Please note that the term "fractionated" was suggested by the Examiner in her Office Action. To further confirm that these recitations were in line with the Examiner's position in the Office Action, Applicants' representative initiated a telephone interview that was made of record, the substance of which is stated above. In addition, the Examiner clearly states that the 35 U.S.C 102 (b) rejection of the claims is due to the Markush recitations. *See supra.* In conforming with after-final amendment practice and in reliance on the statements made by the Examiner in her Office Action and subsequent Interview Summary Record, Applicants strongly assert that they have met the relevant portions of 37 C.F.R 116(b), and that the Examiner erred in denying entry of the after-final Amendment and that entry of the after-final Amendment would have resulted in the allowance of the claims in dispute.

Furthermore, as stated in the MPEP, "The first search should be such that the examiner need not ordinarily make a second search of the prior art, unless necessitated by amendments to the claims by the applicant in the first reply, except to check to determine whether any reference which would appear to be substantially more pertinent than the prior art cited in the first Office action has become available subsequent to the initial prior art search. The first search should cover the invention as described and claimed, *including the inventive concepts toward which the*

claims appear to be directed. It should not be extended merely to add immaterial variants (emphasis added)." *See* MPEP §904 (Jul 2008). Applicants initially presented the claim recitation of "fractionation" in response to the Examiner's position that "non-hydrolyzed extract" lacked antecedent basis and constituted new matter. As the discussions of direct extraction versus hydrolyzed extraction became a focal point in distinguishing the present invention from that of the prior art, Applicants utilized the term "fractionation" in their claim recitation because its definition was adequately supported by the specification. *See* Examiner's Office Action at 4 (May 30, 2007); Applicants' Response at 10 (Nov. 30, 2007) and *supra*. Factually, the recitation was accepted by the Examiner as evidenced in her Office Action where she states "It would appear that Applicant intends to direct the subject matter of the claimed invention to a biologically active extract comprising a *fractionated* (emphasis added) extract from at least one plant selected from the claim-designated Markush group recited in Claim 1." *See* Examiner's Office Action at 2 (Mar 28, 2008). The statement by the Examiner provides direct evidence that "fractionating" was understood as defined by the Applicants' specification, recited in the claims and supported by MPEP §904. This is further substantiated by the statement presented in the Interview Summary Record. *See supra*. Therefore, the Applicants assert that the Examiner's statements provide implicit evidence that the amendments to the claims changing "fractionating" to "fractionated" are inventive concepts towards which the claims are directed, and are also immaterial variants that would not necessitate further searching. *See supra*. Furthermore, Applicants' amendments to the claims were made in a good faith reliance of the statements in the Examiner's Office Action and in the Telephone Interview Summary Record stating that such amendments would result in an allowance of the claims. In addition to the MPEP *supra*, Applicants respectfully submit that the age of electronic searching substantially dilutes the

Examiner's position that a mere tense change of a word necessitates additional searching to the level that will deny entry of an amendment.

3. Applicants contend that claims 1, 11, 30 and 38 are not anticipated by Applicants' prior art since the Examiner acknowledges that "the elected species, namely *Napoleonaea imperialis*, the solvent methanol and the seed portion of the plant, was not found..." *See* Office Action 2, line 3 (Mar 28, 2008) (holding that, as a Markush group, the claims are anticipated by Christopher O. Okunji, et al., *supra*, due to Applicants' recitation of *Dracaena arborea*). The claims are argued together. As stated above, Applicants are placing before the Board the claims as recited in the submitted Office Action of July 24, 2008, that limit claim recitation to that acknowledged by the Examiner. See *supra*. This acknowledgement is of particular concern as Applicants have narrowed claim recitation in reliance on the Examiner's position.

In view of the body of evidence provided above, Applicants continue to contend that the Examiner's position is without merit. Therefore, Applicants respectfully submit that the Board overturn the rejection of claims 1, 11, 30 and 38 and hold these claims allowable.

Sincerely,

May 22, 2009
Date

Abanti A. Bhattacharyya, Esq.
Reg. No. 36,681

VIII. CLAIMS APPENDIX

The claims involved in this Appeal are as follows:

1. A biologically active extract comprising a fractionated extract from *Napoleonaea imperialis*, wherein said extract is obtained using an organic solvent, and wherein said biologically active extract is saponin-enriched and exhibits therapeutic anti-leishmanial activity.

11. A biologically active extract according to claim 1, wherein said extract is obtained directly from solvent extraction of powdered seeds of *Napoleonaea imperialis* utilizing said solvent.

30. A biologically active extract according to claim 1, wherein said solvent is methanol, wherein said extract is obtained directly from solvent extraction of powdered seeds of said plant utilizing said solvent.

38. A biologically active extract according to claim 11, wherein said solvent is methanol.

IX. EVIDENCE APPENDIX

The following is evidence entered by the Examiner and relied upon by Appellant in the Appeal, copies of which are attached herein:

A. File History (in order of appearance in Appeal Brief)

1. Applicants' Amendment of July 24, 2008
2. Examiner's Office Action of March 28, 2008
3. Examiner's Advisory Action of August 21, 2008
4. Examiner's Advisory Action October 10, 2008
5. Interview Summary Record of July 24, 2008
6. Applicants' 132 Declaration of December 20, 2006
7. Examiner's Office Action of April 4, 2002
8. Examiner's Office Action of May 30, 2007
9. Applicants' Response of November 30, 2007

B. Prior Art

1. Christopher O. Okunji et al., *Biological Activity of Saponins from Two Dracaena Species*, 404 Adv. Exper. Med. Bio. 415 (1996).

X. RELATED PROCEEDINGS APPENDIX

None

XI. TABLE OF CASES & RELEVANT SECTIONS OF THE MPEP

A. Cited Case Law (in order of appearance in the appeal brief):

1. *Bell Communications Research, Inc. v. Vitalink Communications Corp.*, 55 F.3d 615, 620, 34USPQ 2d 1816, 1819 (Fed. Cir. 1995);
2. *Hoechst Celanese Corp. v BP Chems. Ltd.*, 78 F.3d 1575, 157, 38 USPQ 1126, 1129 (Fed. Circ. 1996).

B. Manual of Patent Examination Procedure Sections (in order of appearance in the appeal brief):

1. MPEP §2107.03;
2. MPEP §904.01;
3. MPEP §2111;
4. MPEP §904.

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF

APPLICANT:	Okunji et al.	DATE:	July 24, 2008
SERIAL NO.:	09/428,203	GROUP ART UNIT:	1655
FILED:	October 27, 1999	EXAMINER:	M. Flood

FOR: PLANT DERIVED ANTI-PARASITIC AND ANTI-FUNGAL COMPOUNDS AND METHODS FOR EXTRACTING THE COMPOUNDS

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir,

The following is an after-final response to the Examiner's office action of March 28, 2008. Applicants respectfully request that the response be entered. Applicants also respectfully request a one month extension of time set to expire on July 28, 2008. A petition for an extension of time, a fee transmittal form and a transmittal form are attached hereby. The Commissioner is hereby authorized to charge any fees that may be required in connection with the filing of this request, as well as credit any overpayment, to U.S. Army Medical Research and Materiel Command, Deposit Account Number 210380.

(1) A marked copy of the claims, with amendments, begins on page 3.

(2) A clean copy of the claims, with amendments, begins on page 5.

(3) Remarks begin on page 7.

Marked Copy of the Claims:

1. (currently amended) A biologically active extract comprising a fractionated ~~fractionation~~ extract from ~~at least one plant selected from the group consisting of *Aframomum aulocacarpus*, *Aframomum danielli*, *Dracaena arborea*, *Eupatorium odoratum*, *Glossocalyx brevipes* and~~ *Napoleonaea imperialis*, wherein said extract is obtained using an organic solvent, and wherein said biologically active extract is saponin-enriched and exhibits therapeutic anti-leishmanial activity.

2 through 10 (cancelled)

11. (previously presented) A biologically active extract according to claim 1, wherein said extract is obtained directly from solvent extraction of powdered seeds of *Napoleonaea imperialis* utilizing said solvent.

12 through 29 (cancelled)

30. (currently amended) A biologically active extract according to claim 1, wherein said solvent is ~~selected from a group consisting of hexane, chloroform, ethyl acetate and~~

methanol, wherein said extract is obtained directly from solvent extraction of powdered seeds of said plant utilizing said solvent.

31 through 37 (cancelled).

38. (previously presented) A biologically active extract according to claim 11, wherein said solvent is methanol.

39 through 40 (cancelled).

A Clean Copy of the Claims:

1. (currently amended) A biologically active extract comprising a fractionated extract from *Napoleonaea imperialis*, wherein said extract is obtained using an organic solvent, and wherein said biologically active extract is saponin-enriched and exhibits therapeutic anti-leishmanial activity.

2 through 10 (cancelled)

11. (previously presented) A biologically active extract according to claim 1, wherein said extract is obtained directly from solvent extraction of powdered seeds of *Napoleonaea imperialis* utilizing said solvent.

12 through 29 (cancelled)

30. (currently amended) A biologically active extract according to claim 1, wherein said solvent is methanol, wherein said extract is obtained directly from solvent extraction of powdered seeds of said plant utilizing said solvent.

31 through 37 (cancelled).

38. (previously presented) A biologically active extract according to claim 11, wherein said solvent is methanol.

39 through 40 (cancelled).

Remarks:

(1) Applicants wish to thank Examiner Flood for the telephonic interview of July 24, 2008. Applicants respectfully request that this after-final amendment be entered as it places the present application in condition for allowance for the reasons given below.

(2) The Examiner states that "The elected species, namely *Napoleonaea imperialis*, the solvent methanol and the seed portion of the plant, was not found." See Examiner's Action of March 28, 2008, page 2.

Applicants have amended claims 1, 11 and 30 to only recite the species *Napoleonaea imperialis*, the seed extracts of the species and the organic solvent, methanol. Applicants have cancelled pending claims 2 through 10, 12 through 29, 31 through 37 and 39 through 40 to better recite the invention of the present applications. Applicants, however, reserve their rights to file a divisional application directed to all of the cancelled claims. Based on the Examiner's acknowledgment and telephonic interview, it is the Applicants' position that the amendments to claims 1, 11 and 30 place pending claims 1, 11, 30 and 38 in condition for allowance.

(3) Applicants acknowledge the Examiner's rejection of claims 1, 11, 12, 30, 31 and 38 under 35 USC 112 2nd paragraph. Applicants have amended claim 1 to better recite the invention and overcome the rejection of the claims. Applicants discussed the claim amendments in the telephonic interview with the Examiner of record. Based on the Examiner's action and the telephonic interview, it is the Applicants' position that the amendment to claim 1 overcomes the 112 2nd paragraph rejection and places the claims in condition for allowance.

(4) Applicants acknowledge the Examiner's rejection of claims 1, 12, 30 and 31 under 35 USC 102(b) as being anticipated by Okunji, et al.

Based on the amendments to the claims above, the Examiner's acknowledgement discussed in (1) above and the telephonic interview, the rejection of the claims is moot and a discussion by Applicants of the Examiner's rejection is no longer relevant.

Early allowance of claims 1, 11, 30 and 38 is respectfully solicited.

The Examiner is respectfully requested to send all correspondences to: Elizabeth Arwine, Esq.; Office of the Staff Judge Advocate; U.S. Army Medical Research & Materiel Command;

504 Scott Street, Fort Detrick, Maryland 21702-5012; Attn: MCMR-JA (Ms. Arwine).

Please direct any questions regarding this case to Ms. Abby Bhattacharyya, Esq. at (410) 964-9553.

July 29, 2008
Date

Abanti A. Bhattacharyya, Esq.
Reg. No. 36,681

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/428,203	10/27/1999	CHRISTOPHER O. OKUNJI	003/172/SAP	4366

7590 03/28/2008

ELIZABETH A. ARWINE
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EXAMINER	
FLOOD, MICHELE C	
ART UNIT	PAPER NUMBER
1655	

MAIL DATE	DELIVERY MODE
03/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/428,203	OKUNJI ET AL.	
	Examiner	Art Unit	
	Michele Flood	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35 and 38* is/are pending in the application.

4a) Of the above claim(s) *2-10,13-29 and 32-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,11,12,30,31 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment is made of the receipt and entry of the amendment filed on November 30, 2007 with the cancellation of Claim 40.

The elected species, namely *Napoleonaea imperialis*, the solvent methanol and the seed portion of the plant, was not found; therefore, the elected invention was searched to the extent that the next species was found.

Claims 1, 11, 12, 30, 31 and 38 are under examination.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 11, 12, 30, 31 and 38, as amended, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Newly applied as necessitated by amendment.

Claim 1 is rendered indefinite by the phrase "A biologically active extract comprising a fractionation extract" because it is not clear as to the subject matter to which Applicant intends to seek patent protection. For example, plant material may be initially extracted with either water or methanol as a solvent in the making of a crude plant extract followed by subjecting the crude plant extract to fractionation with one or more solvents of increasing polarity or increasing strength. It would appear that

Applicant intends to direct the subject matter of the claimed invention to a biologically active extract comprising a fractionated extract from at least one plant selected from the claim-designated Markush group recited in Claim 1. The lack of clarity renders the claim ambiguous.

All other cited claims depend directly or indirectly from rejected claims and are, therefore, also, rejected under U.S.C. 112, second paragraph for the reasons set forth above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 12, 30 and 31, as amended, are rejected under 35 U.S.C. 102(b) as being anticipated by Okunji et al. (U). Newly applied as necessitated by amendment.

Applicant claims a biologically active extract comprising a fractionation extract from at least one plant selected from the group consisting of *Aframomum aulocacarpus, Aframomum danielli, Dracaena arborea, Eupatorium odoratum, Glossocalyx brevipes* and *Napoleonaea imperialis*, wherein the extract is obtained using an organic solvent, and wherein the biologically active extract is saponin-enriched and exhibits therapeutic anti-leishmanial activity. Applicant further claims a biologically active extract according to claim 1, wherein the extract is from at least one of roots, stem, bark, leaves, fruits or

seeds from the plant; wherein the solvent is selected from a group consisting of hexane, chloroform, ethyl acetate and methanol wherein the extract is obtained directly from solvent extraction of powdered seeds of the plant utilizing the solvent. Applicant further claims a biologically active extract according to claim 11, wherein the solvent is methanol.

Okunji teaches a saponin-enriched fraction of a methanol extract of powdered seed pulp obtained from *Dracaena arborea* (*see* abstract). On page 417, under "*Extraction and Isolation Protocol*", Okunji teaches that the powdered pulp plant material was directly extracted with methanol and that 'a portion of the methanol extract was first partitioned between chloroform-methanol-water mixture to yield a saponin-enriched lower organic layer which was concentrated to dryness *in vacuo* and lyophilized'. Okunji further teaches fractionation of the crude active saponin extract to obtain three spirostanol saponins, designated spiroconazole A, B and C. Okunji demonstrates that spiroconazole A exhibits anti-leishmanial activity (see Figures 4 and 5).

The reference anticipates the claimed subject matter.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele Flood whose telephone number is 571-272-0964. The examiner can normally be reached on 7:00 am - 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on 571-272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michele Flood
Primary Examiner
Art Unit 1655

MCF
March 24, 2008
/Michele Flood/
Primary Examiner, Art Unit 1655

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/428,203	10/27/1999	CHRISTOPHER O. OKUNJI	003/172/SAP	4366

7590 08/21/2008

ELIZABETH A. ARWINE
USAMRMC
FORT DETRICK
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FREDERICK, MD 21701

EXAMINER	
FLOOD, MICHELE C	
ART UNIT	PAPER NUMBER
1655	

MAIL DATE	DELIVERY MODE
08/21/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	09/428,203	OKUNJI ET AL.	
	Examiner	Art Unit	
	Michele Flood	1655	

Advisory Action Before the Filing of an Appeal Brief

Application No.	Applicant(s)	
09/428,203	OKUNJI ET AL.	
Examiner	**Art Unit**	
Michele Flood	1655	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 24 July 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,11,12,30,31 and 38*.
   Claim(s) withdrawn from consideration: *2-10,13-29 and 32-35*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: Applicant's arguments are directed to limitations not entered.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Michele Flood/
Primary Examiner, Art Unit 1655

Continuation of 3. NOTE: Applicant's insertion of the limitation "fractionated" would require further search and/or consideration.

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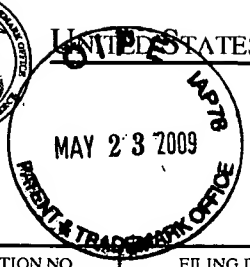

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/428,203	10/27/1999	CHRISTOPHER O. OKUNJI	003/172/SAP	4366

7590 10/10/2008

ELIZABETH A. ARWINE
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EXAMINER	
FLOOD, MICHELE C	
ART UNIT	PAPER NUMBER
1655	

MAIL DATE	DELIVERY MODE
10/10/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	09/428,203	OKUNJI ET AL.	
	Examiner	Art Unit	
	Michele Flood	1655	

Advisory Action Before the Filing of an Appeal Brief

Application No.	Applicant(s)	
09/428,203	OKUNJI ET AL.	
Examiner	**Art Unit**	
Michele Flood	1655	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 21 August 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

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   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
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6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
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   The status of the claim(s) is (or will be) as follows:
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   Claim(s) objected to: _____.
   Claim(s) rejected: *1,11,12,30,31 and 38*.
   Claim(s) withdrawn from consideration: *2-10,13-29 and 32-35*.

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10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: Applicant's arguments are directed to limitations not entered.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Michele Flood/
Primary Examiner, Art Unit 1655

Continuation of 3. NOTE: Applicant's insertion of the limitation "fractionated" would require further search and/or consideration122

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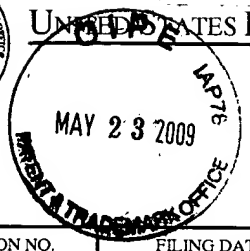

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/428,203	10/27/1999	CHRISTOPHER O. OKUNJI	003/172/SAP	4366

7590 07/28/2008

ELIZABETH A. ARWINE
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FREDERICK, MD 21701

EXAMINER	
FLOOD, MICHELE C	
ART UNIT	PAPER NUMBER
1655	

MAIL DATE	DELIVERY MODE
07/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Interview Summary

Application No.	Applicant(s)	
09/428,203	OKUNJI ET AL.	
Examiner	**Art Unit**	
Michele Flood	1655	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Michele Flood*. (3)_____.

(2) *Abby Bhattacharyya*. (4)_____.

Date of Interview: *24 July 2008*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: _____.

Claim(s) discussed: *All pending claims*.

Identification of prior art discussed: *Okunji et al.*.

Agreement with respect to the claims f)☒ was reached. g)☐ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Applicant's representative, Abby Bhattacharyya, proposes limiting the species recited in Claim 1 to Napoleonaea imperialis and cancelling Claims 2-10, 12-29 and 31-35. Amending the claims as discussed would appear to obviate the rejections of record and place Claims 1, 11, 30 and 38 in condition for allowance absent discovery of prior art that reads on the claimed subject matter.*\.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

/Michele Flood/
Primary Examiner, Art Unit 1655
Examiner's signature, if required

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	09/428,203	OKUNJI ET AL.	
	Examiner	Art Unit	
	Michele Flood	1655	

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	)	
	)	
APPLICANT: Okunji, et al.	)	DATE:
	)	
SERIAL NO.: 09/428,203	)	GROUP ART UNIT: 1651
	)	
FILED: October 27, 1999	)	EXAMINER: M. Flood
	)	
FOR: PLANT DERIVED ANTI-PARASITIC AND ANTI-FUNGAL COMPOUNDS AND METHODS FOR EXTRACTING THE COMPOUNDS	)	09/428,203 (Okunji, et al.) Attachment A (14 Pages)

RULE 132 DECLARATION

1. I, Christopher O. Okunji, do hereby declare that:

2. I am a Ph.D. Pharmacognosist, Senior Research Associate at LTS Corporation, Bethesda, Maryland.

During the patent application process my employment as Senior PhD Research Pharmocognosist, was as follows:

Date	Patent Information activities	Employment (agency paid salary)
1990-1993	invention conceived	University of Nigeria, Nsukka
03-1993-1996	invention developed first drafted	National Science Foundation and International cooperative Biodiversity Grant (ICBG), USA
1996-	invention disclosed (provisional)	ICBG - fund from NIH
	invention submitted as PTO application	ICBG - fund from NIH
06-03-2005	invention prosecution	ICBG (left WRAIR)
06-04-2004 10-23-2005	"	self-employed
10-24-2005 04-28-2006	"	Rutgers University, Biotech Center, NJ
05-01-2006 – present	"	LTC Corporation (Fed contractor)

3. I wish to state that the references of record by researchers/scientists (Mbah, et al., and Ekpendu, et al.) were made known to me, and that my work as stated in the above-identified patent application is substantially different from the art of record. My work on *Napoleonaea* is part of my Ph.D. dissertation, specifically the use of seeds vs. that of other plant parts such as extracts. (see detail item 6). To illustrate the above points, my research interest on the genus *Napoleonaea* started as far back as 1983 when I screened this plant for molluscicidal activity. My Ph.D. dissertation in 1987, entitled "Molluscicidal and Antifungal Properties of Some Nigerian Medicinal Plants,"
http://www.unn-edu.net/postgrad/pg fac of pharm sci.htm
identified *Napoleonaea vogeli* auct. (Fam. Lecythidaceae; synonyms: *Napoleonaea imperialis* P. Beauv.) as potential plant molluscicides. Further screening of this plant for antileishmanial activity in 1993 identified *Napoleonaea imperialis* seeds as having a promising antileishmanial activity. Bioassay guided-chromatographic fractionation of *Napoleonaea imperialis* seeds yielded imperialisides (A-C).

4. That the work of Mbah, et al., was on the antibacterial activity of extracts from leaves, stem-bark, root and root-bark

of *Napoleonaea imperialis* without specific identification of any phytochemical constituent, while my work on the seed specifically identified three antileishmanial compounds belonging to the class saponin. Please note that the conclusion of the Mbah, et al., reference states: "...the absence of toxic affects for the flavonoids and triterpenoids is very important for testing their eventual (emphasis added) activity on human lymphocytes." No conclusive data on human activity had been established. Thus, the use of ethanol in extraction is insignificant to Dr. Mbah, et al.

5. Similarly, Dr. Ekpendu's group studied "hexane, ethyl acetate and methanol extracts of Napoleonaea imperialis, obtained from the root bark, not the extracts from the seeds themselves." As established in my patent application, the seeds were chosen by my group to obtain biologically active extracts showing antileishmanial activity.

6. A critical review of the referenced publications on *Napoleonaea imperialis* P.Beauv(Lecythidaceae) by Ekpendu *et al* (1998) and Kapundu *et al* (1980) revealed the following observations; first, the two groups of investigators were chemists and therefore were more interested on the chemistry of this plant rather than their biological or therapeutic

properties. Secondly, neither Ekpendu nor Kapundu screened for biological or pharmacological activities of the constituents of this plant. Also both groups used similar methods in their chemical investigation of the major constituents of *N. imperialis* known as saponins. In all, both referenced papers the saponins were first hydrolyzed before isolation and chemical identification of the constituents. It is remarkable to note that both groups worked on the hydrolyzed products (sapongenols/sapogenins/aglycones/genin) instead of the intact plant constituents (saponins). The implication of these approaches will be discussed in details. Some investigators adopted hydrolysis method because it eliminates the sugars resulting to simpler compounds. The product of hydrolysis is simpler, yielding lower molecular weight compounds, less polar, less complex structurally and easy to handle.

In contracts, as a pharmacognosist, I was particularly interested in the un-hydrolyzed, naturally occurring and pharmacological/ biological active plant constituents. My approach eliminated all processes of hydrolysis for compounds submitted for biological testing. In fact only naturally occurring pharmacologically active compounds were pursued further rather than hydrolyzed products. Bioassay directed-chromatographic fractionations of active extracts were

undertaken leading to the isolation of naturally occurring saponins hereby eliminating art fats.

To fully appreciate the distinction made above between the approaches adopted by Ekpendu and Kapundu while investigating *N. imperialis* seeds and root-bark respectively and that of mine investigating the seeds of *N. imperialis*, it is important to examine the constituents of this plant. Our present knowledge on *N. imperialis* indicated that the major constituents of this plant are the saponins, although there is very scanty information available in the literature on this plant.

Saponins are high-molecular-weight glycosides, consisting of a **sugar moiety** linked to a triterpene or steroid (**aglycone**).

Therefore, Saponin = Sugar + Aglycone (triterpene or steroid).

All saponins have in common the attachment of one or more sugars to the aglycone. Saponins are extremely widely distributed in the plant kingdom. Saponins occur in some plants which are used as human food. The list of biological activity associated with saponins is very long.

Saponin contents of different morphological plant part:

Plant secondary metabolites such as saponins, alkaloids, flavonoids etc have been report to vary in their distribution in different plant parts. In these examples, saponin contents have been reported to vary depending on factors such as the cultivar, the age, the physiological state and the geographical location of the plant (Hostettmann and Maraton, (1994)). Considerable variation in composition and quantity of saponins in vegetable material from different places, as documented for *Lonicera japonica* (Caprifoliaceace) has been reported (Kawai *et al.* 1998).

The saponin distribution among the organs of a plant may vary considerably. In the garden marigold (*Calendula officinalis*, Asteraceae), for example saponins with a glucuronic acid moiety at C-3 of oleanolic acid are founding the flowers, while a glucose moiety at the same position is found in the saponins from the roots (Lutomski, 1983; Vidal-Ollivier et al. 1989a,b). The flowers contain 3.57% saponins, while the roots have 2.55% of their dry weight in the form of saponins (Isaac, 1992). Ginsenoside levels in Panax ginseng (Araliaceae) are lowest in the leafstalks and stem (0.77%), intermediate in the main root (1.3%) and lateral roots (3.5%) and highest in the leaves (5.2%) and root hairs (6.1%) (Koizumi *et al.* 1982).

The above examples address some of the examiner's concerns with regards to the composition of different parts of the plant parts; root-barks vs seeds. Our work on Dracaena species revealed that very high saponin content are found mostly in the seeds (Okunji *et al* 1996)

Problems Associate with Hydrolysis: Method adopted by Ekpendu and Kapundu

Numerous chemical reactions and methods have been employed for breaking down saponins into smaller units for more ready analysis (Kitagawa 1981), one of such method is acid hydrolysis.

It is believed that once acid hydrolysis is completed, then the aglycone will be separated and identified. Many chemists including Ekpendu *et al* (1998) and Kapundu *et al* (1980) adopted hydrolysis of saponins prior to chemical characterization of plant constituents. However, there are some significant concerns such as artifacts formation, not being able to obtain genuine aglycone, possibility of epimerization, transformation etc. The following paragraphs will illustrate the above pitfalls in detail.

It has been reported that acid hydrolysis is not without risk because prolonged heating with an inorganic acid can give rise to complications involving artifact formation, low yields

and low selectivity (Tschesche and Wulff, 1972; Kitagawa, 1981). This is true not only of triterpene saponins but also of steroid saponins and saponins from marine organisms (Kitagawa *et al.* 1985b), often making the job of structure elucidation very complicated. A typical example from a study of the effects of various hydrolytic procedure on the sapogenin profile of soya saponins has shown that soyasapogenols B_1, C, D and E are probably formed as artifacts on aqueous hydrolysis of soya flour with hydrochloric acid in ethanol (Ireland *et al.* 1987). The true aglycones, soyasapogenols A and B are obtained by hydrolysis with sulphuric or hydrochloric acid in anhydrous methanol (Ireland and Dziedzic, 1986). Another problem arises during the acid hydrolysis of oleanolic acid and hederagenin glycosides in dioxin, giving rise to possible formation of lactone (Hiller *et al.* 1987). Similarly, Sulphuric acid on hydrolysis of hovenosides (glycosides of jujubogenin) gave a lactone, ebelin lactone (Inoue *et al.* 1978).

It is sometimes very difficult to obtain the genuine aglycones from the parent saponins. This problem is especially acute for the triterpenes containing a 13β, 28-oxide structure. Tscheshe and coworkers stated that it took a long time, for example, before the aglycone cyclamiretin A of cyclamen (from the tubers of *Cyclamen europaeum,* Primulaceae) was completely characterized (Tscheshe *et al.* 1966). Another example is the

case for other 13β, 28-oxide aglycones (protoprimulagenin A), saikogenin F, etc.), it could be easily ring-opened by acid to the corresponding 12-en-28-alcohol. Similarly Primulaginin A is most probably an artifact produced during hydrolysis of saponins containing protoprimulagenin A as aglycone (Tscheshe *et al.* 1983). It should be noted here, however, that not all 12-en-28-alcohol aglycones are artifacts.

On hydrolysis, an acid-catalysed double-bond migration in triterpenes can also occur. For example, some olean-12-enes are isomerized to olean-13(18)-enes with hydrochloric acid in aqueous ethanol (Kubota *et al.* 1969). Quallaic and echinocystic acids are both isomerized to the corresponding olean-13(18)-enes under these conditions (Kubota *et al* 1969).

Epimerization is possible during acid hydrolysis, as shown by the conversion of arjungenin (from the corresponding 28-glycoside) to tomentosic acid. This transformation proceeds through the pathway described by Mahato *et al.* 1990 and confirmed by the isolation of the intermediate lactone.

The transformation of cochalic acid to echinocystic acid is another example. It involves an epimerization at the 16-OH group and probably also occurs via a 28 → 16 lactone (Mahota *et al.* 1990).

These are very few examples of potential risk of isolating art facts instead of naturally occurring plant constituents

associated when adopting acid hydrolysis in duringphytochemical investigations. It is possible that some of the Ekpendu's compounds were artifacts. The compounds isolated by my method have been replicated several times.

In conclusion; as reported Ekpendu *et al* (1998), hydrolysis of both ethyl acetate and methanol extracts were undertaken leading to the isolation of series of less polar compounds when compared with unhydrolyzed compounds. Similarly, control hydrolysis was carried out by Kapundu *et al* (1980) leading to characterization of new "prosapogenins" napoleogenol and napoleogenin which were less polar relative to un- hydrolized counterpart.

The approach adopted by both Ekpendu *et al* (1998) and Kapundu *et al* (1980) differ significantly from mine in that in my investigation, no acid hydrolysis was used instead intact saponins were isolated and characterized. In addition biological testing was carried out leading to the identification of bioactive compounds. The distribution of secondary metabolites in different plant parts has been discussed above. The results showed that different constituents have been isolated from different plant parts.

7. These facts would have been corroborated by Dr. Ekpendu, who is known to me. However, due to extreme hardships and all attempts to contact Dr. Ekpendu failed even during my several trips to Nigeria between 2000-2003. These hardships included economic and financial constraints, lack of communication or national database or national phonebook etc. Additionally several attempts to contact students (who had worked on the experiments leading to Dr. Ekpendu's results) also failed. Due to the lack of proper communication facilities and the absence of demographic databases, any information on these students were unattainable since they had subsequently graduated.

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I further declare under penalty of perjury, pursuant to the laws of the United States of America, that the foregoing is true and correct, and that this declaration was executed by me on December 19, 2006, at Silver Spring Maryland.

Christopher O. Okunji 12/19/2006

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/428,203	10/27/1999	CHRISTOPHER O. OKUNJI	003/172/SAP	4366

7590 04/04/2002

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EXAMINER
FLOOD, MICHELE C

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 04/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/428,203	Okunji et al.
Examiner	**Art Unit**
Michele Flood	1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *Apr 2, 2001*

2a)☐ This action is **FINAL.** 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideratio

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some* c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)

16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18)☐ Interview Summary (PTO-413) Paper No(s). _____

19)☐ Notice of Informal Patent Application (PTO-152)

20)☐ Other:

DETAILED ACTION

Applicant's election without traverse of Claims 1-12 in Paper No. 7 is acknowledged, and the remaining claims are withdrawn from further consideration by the Examiner as an non-elected group drawn to another invention. Acknowledgment is also made of Applicant's election of the species *Napoleonaea imperialis*.

Specification

The disclosure is objected to because of the following informalities: on page, 29, line 30, there is apparent text missing after the word "and". Appropriate correction is required.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for ethyl acetate and methanolic extracts of the seeds of *Napoleonaea imperialis* which exert antileishmanial or antifungal activity, does not reasonably provide enablement for exerting any and all biological activities, wherein the plant extract is prepared using any and all solvents, and any all plant parts thereof. The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a biologically active extract from at least one plant selected from the group consisting of *Aframomum aulocacarpus, Aframomun danellii, Dracaena arborea, Eupatorium odoratum, Glossocalyx brevipes* and *Napoleonaea imperialis.* The claims are further drawn to a biologically active extract, wherein said extract is from *Napoleonaea imperialis.* The claims are further drawn to a biologically active extract, wherein said extract is from at least one of roots, stem bark, leaves, fruits or seeds from said plant.

Applicant has demonstrated ethyl acetate and methanolic extracts of the seeds of *Napoleonaea imperialis*, wherein effective amounts of the extracts or compounds exerted either antileishmanial, antifungal or antimalarial activities. Applicant demonstrated that the extracts and pure compounds obtained from said extract showed significant activity *in vivo* on hamster challenged with cutaneous or visceral *Leishmania* isolates. Applicant has demonstrated *in vitro* antifungal activity of said extract comprising the compound Laba-8(17), 12-diene-15, 16-dial (AD-1) against *Cladosporium cucumerinum*, as illustrated in Figure 1. Finally, Applicant has demonstrated *in vitro* antimalarial activity of said extract comprising the compound Laba-8(17), 12-diene-15, 16-dial (AD-1) against *Plasmodium falciparum*, as illustrated in Table 2. Thus, the examiner notes that Applicant has demonstrated *in vitro* and/or *in vivo* antileishmanial, antifungal or antimalarial activities of compound AD-1 obtained from a seed extract of *Napoleonaea imperialis*, using either ethyl acetate or methanol.

While the claims do not expressly direct the method of using an extract of *Napoleonaea imperialis* to treat leishmanial, antifungal, malarial, and fungal disease in humans, the specification teaches delivering the extract to hamsters bearing either malarial parasite clones or promastigote leshmanial forms by oral, intramuscular and subcutaneous routes of administration. Moreover, the specification suggests the use of the instantly claimed extract in the development of new and effective therapeutic agents for the treatment of human diseases in tropical and African countries. The examiner notes that the specification is particularly silent to the use of the instantly claimed extract as a therapeutic agent in the chemotherapy of protozoal diseases. However, it is noted that the specification teaches the administration of extracts of *Napoleonaea imperialis* to hamsters, and that Applicant stresses, "In Africa, traditional medicine with herbal treatment has a long history and is used routinely used in medical care, " on page 26, lines 27-30. Inventions targeted for anti-protozoal drugs bear a heavy responsibility to provide supporting evidence because of the unpredictability in biological responses to therapeutic treatments. The standard of enablement is higher for such inventions because effective treatments for disease conditions are relatively rare, and may be unbelievable in the absence of supporting evidence.

Claims drawn to compositions intended for the administration to either mammals or humans generally require supporting evidence which clearly define the ingredients or constituents contained therein because of the unpredictability in biological responses to therapeutic treatments. In order to enable the skilled artisan to practice the invention as claimed, applicant would have to demonstrate the functional effect and describe the therapeutic effective amounts of extract

intended for a therapeutic treatment. There is no guidance in the specification, other than an ethyl acetate or methanolic extract of the seeds of *Napoleonaea imperialis*, which Applicant has shown to demonstrate antileishmanial, antifungal or antimalarial activities, wherein said extract comprises compound AD-1. According, it would take undue experimentation without a reasonable expectation of success to determine which plant extracts would exert which biological activities, wherein the plant extract is prepared using any and all solvents, and any all plant parts thereof other than those demonstrated as discussed above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rendered vague and indefinite by the term "extract" because this term, in and of itself, does not adequately delineate its metes and bounds. This term is best defined as a product-by-process since product-by-process claims are intended to define products which are otherwise difficult to define (and/or distinguish from the prior art). For example, is the extract obtained via extraction with water, a polar solvent, a non-polar solvent, an acid or base, a squeezed extract, or something else? In addition, from what part(s) of the plant is the extract obtained? It is well

accepted in the herbal art that extraction with one of various distinct solvents, as well as from particular parts of therapeutic plants, has a profound impact on the final product with respect to the presence, absence, amounts, and/or ratios of active ingredients therein and, thus, its ability to provide the desired functional effect(s) instantly claimed and/or disclosed. Since the extract itself is clearly essential to the claimed invention, the step(s) by which the claimed extract is obtained are also clearly essential and, therefore, must be recited in the claim language itself (i.e., as a product-by-process). Please note that although the claims are interpreted in light of the specification, critical limitations from the specification cannot be read into the claims (see, e.g., *In re* Van Guens, 988 F.2d 1181, 26 PSPG2d 1057 (Ded. Cir. 1991)). Accordingly, without the recitation of all these critical limitations as set forth above, the claims do not adequately define the instant invention.

All of the claims are rendered vague and indefinite by the phrase "biologically active extract" because it is uncertain as to which biologically activity Applicant refers. Does the "biologically active extract" exert antibacterial, antifungal, nematocidal or antiparasitic activity? The lack of clarity makes the claim ambiguous.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 11-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Mbah et al. (U).

Applicant claims a biologically active extract from at least one plant selected from the group consisting of *Aframomum aulocacarpus, Aframomun danellii, Dranaena arborea, Eupatorium odoratum, Glossocalyx brevipes* and *Napoleonaea imperialis.* Applicant further claims a biologically active extract, wherein said extract is from *Napoleonaea imperialis.* Applicant further claims a biologically active extract, wherein said extract is from at least one of roots, stem bark, leaves, fruits or seeds from said plant.

Mbah teaches an extract of the leaves, stems, stem bark, roots and root bark of *Napoleonaea imperialis* which exerts antimicrobial activity against bacterial species. The reference anticipates the claimed subject matter.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele Flood whose telephone number is (703) 308-9432. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196 or the Supervisory Patent Examiner, Michael Wityshyn whose telephone number is (703) 308-4743.

MCF

April 27, 2001

CHRISTOPHER R. TATE
PRIMARY EXAMINER

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/428,203	10/27/1999	CHRISTOPHER O. OKUNJI	003/172/SAP	4366

7590 05/30/2007

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EXAMINER	
FLOOD, MICHELE C	
ART UNIT	**PAPER NUMBER**
1655	

MAIL DATE	DELIVERY MODE
05/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/428,203	OKUNJI ET AL.	
	Examiner	Art Unit	
	Michele Flood	1655	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35,38 and 40* is/are pending in the application.

4a) Of the above claim(s) *2-10,13-29 and 32-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,11,12,30,31,38 and 40* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment is made of the receipt of the declaration filed under Rule 1.132 by Christopher O. Okunji, Ph. D on December 20, 2006.

Applicant's arguments, as well as the arguments set forth in the 1.132 Rule Declaration of Dr. Okunji, have been fully considered and found persuasive. Therefore, the rejection made under 35 U.S.C. 102(b) as being anticipated by the teachings of Ekpendu et al. (U), as forth in the previous Office action is vacated herein.

Response to Arguments

Election/Restrictions

Applicant's election with traverse of the following species: *Napoleonaea imperialis,* the solvent methanol and the seed portion of the plant, in the reply filed on April 12, 2007 are acknowledged. Further acknowledgment is made of Applicant's indication that the elected invention is readable on Claims 1, 11, 12, 30, 31, 38 and 40 are under examination.

The traversal is on the grounds that a search for plants exhibiting anti-leishmanial activity will invariably include a search for *N. imperialis*; that search for anti-leishmanial activity of *N. imperialis* and all portions of a plant; and; that a search for solvents will include others including those recited in the claims of the present invention. However, this is not found persuasive because the claim-designated members of the recited Markush group of Claim 1 are characterized by divergently different botanical extracts; and the search for one of the plant members does not require the search for any of the

other plant members. For instance, a search for *N. imperialis* would not require a search of any of *Aframomum aulocacarpus, Aframomum daneilli, Dracaena arborea, Eupatorium odoratum* and *Glossocalyx brevipes*. This is also not found persuasive because the claim-designated members of the recited Markush group of Claim 12 are characterized by divergently different botanical parts of the plant; and, the search for one plant part, such as a root, would not require the search for another plant, such as a flower or petal or any other aerial plant part. This is also not found persuasive because the claim-designated members of the recited Markush group of Claim 30 are characterized by divergently different chemical constituents; and, a search for one solvent would not require a search for another solvent type. Moreover, additional search terms would be required for a thorough search of the claimed products, thus resulting in a larger more burdensome search for the examiner, especially since the claimed products comprise numerous permutations of numerous ingredients contained therein.

The requirement is still deemed proper and is therefore made FINAL.

The claims have been examined, insofar, as they read on the elected invention.

Claims 1, 11, 12, 30, 31, 38 and 40 are under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11, 30, 31, 38 and 40 are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide prior support or antecedent basis for the language "a non-hydrolyzed extract" in Claims 11 and 30. The claims as set forth in the amendment filed on December 20, 2006 now recite a "a non-hydrolyzed extract". However, the specification as originally filed provides does not preclude compositions that are not a "a non-hydrolyzed extract" *per se*.

Insertion of the above mentioned claim limitation has no support in the as-filed specification. The insertion of the limitation is a new concept because it neither has literal support in the as-filed specification by way of generic disclosure, nor are there specific examples of the newly limited genera which would show possession of the concepts for a composition comprising a non-hydrolyzed methanol extract from powdered seeds of *Napoleonaea imperialis* with regard to Claims 11 and 30. There is not sufficient support for the new aforementioned genera/genus to preclude compositions that are not a "a non-hydrolyzed extract". This is a matter of written description, not a question of what one of skill in the art would or would not have known. The material within the four corners of the as-filed specification must lead to the generic concept. If it does not, the material is new matter. Declarations and new references

cannot demonstrate the possession of a concept after the fact. Thus, the insertion of the above mentioned claim limitation is considered to be the insertion of new matter for the above reasons.

As the above-mentioned claim limitation could not be found in the present specification, the recitation of the claim limitations is deemed new matter; and, therefore it must be omitted from the claim language, unless Applicant can particularly point to the specification for literal support.

It is noted that because claims 31, 38 and 40 depend either directly or indirectly upon Claims 11 and 30, these claims necessarily contain all of the limitations of Claim 11 or Claim 30 and therefore also contain new mater and are properly rejected under this statue.

Legal Standard for Anticipation/Inherency Under - 35 USC § 102

To anticipate a claim under 35 US.C. 102(b), a single prior art reference must place the invention in the public's possession by disclosing each and every element of the claimed invention in a manner sufficient to enable one skilled in the art to practice the invention. *Scripps Clinic & Research Foundation v. Genetech, Inc.,* 927 F.2d 1565, 1576, 18 U.S.P.Q.2d 1001, 1001 (Fed. Cir. 1991); *In re Donahue,* 766 F2d531, 533, 266 U.S.P.Q. 619, 621 (Fed. Cir. 1985). To anticipate, the prior art must either expressly or inherently disclose each limitation of the claimed invention, *MEHL/Biophile Int'l Corp. v. Milgraum,* 192F.3d 1362, 1365, 52 U.S.P.Q.2d 1303, 1303 (Fed. Cir. 1999) (citing to *In re Schreiber,* 128 F.3d 1473, 1477, 44 U.S.P.Q. 1429, 1431 (Fed. Cir.

1997)); *Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1347, 51 U.S.P.Q.2d 1943, 1946 (Fed. Cir. 1999). To inherently anticipate, the prior art, the prior art must necessarily function in accordance with, or include, the claimed limitations. *MEHL/Biophile*, 192 F.3d at 1365, 52 U.S.P.Q.2d at 1303. However, it is not required that those of ordinary skill in the art recognize the inherent characteristics or the functions of the prior art. *Id.* Specifically, discovery of the mechanism underlying a known process does not make it patentable.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 11, 12, 30, 31, 38, as amended, remain, and, newly submitted Claim 40 is rejected under 35 U.S.C. 102(b) as being anticipated by Kapundu et al. (U). Applicant's arguments, as well as the arguments set forth in the 1.132 Rule Declaration of Dr. Okunji, have been fully considered. However, the rejection remains for the reason set forth in the previous Office action and for the reason set forth herein, slightly altered to address the amendment to the claims.

Applicant claims a biologically active extract comprising an extract from at least one plant selected from the group consisting of *Aframomum* aulocacarpus, *Aframomum daneilli, Dracaena arborea, Eupatorium odoratum, Glossocalyx brevipes and Napoleonaea imperialis*, wherein said extract is obtained using an organic solvent; and

wherein said biologically active extract deters leishmanial activity. Applicant further claims a biologically active extract according to claim 1, wherein said extract is a non-hydrolyzed extract from powdered seeds of *Napoleonaea imperialis*; wherein said extract is from at least one of roots, stem bark, leaves, fruits or seeds from said plant; and, wherein said solvent is selected from a group consisting of hexane, chloroform, ethyl acetate and methanol and said extract is a non-hydrolyzed extract. Applicant further claims a biologically active extract according to claim 11, wherein said solvent is methanol; and, wherein said extract is saponin-enriched.

Applicant's main argument is drawn to the idea that the amendment to the claims overcome the anticipatory teachings of Kapundu because the amended claims now encompass subject matter drawn to limitations of leishmanial activity, seed extract, non-hydrolyzed methanol extracts and saponin extracts of *Napoleonaea imperialis*. Applicant further argues that the Examiner has misapplied the inherency doctrine. Thereby, Applicant concludes that the difference between what is taught in the prior art and what is instantly claimed is a methanol extract obtained from the powdered seeds of *Napoleonaea imperialis* comprising saponins and exhibiting activity against leishmania pathogens, and not hydrolyzed seed extracts of the claim-designated plant.

Given the foregoing, Applicant directs the Office to Applicants' 1.132 declaration: "The Examiner's attention is drawn to the Applicants' 132 declaration. Applicants distinguish Kapundu et al., by stating that the adopted hydrolysis of Kapundu et al., incurs 'significant concerns such as artifacts formation, not being able to obtain genuine aglycone, possibility of epimerazation, transformation, etc.' *See*: page 7 of the 132

declaration. This disclosure provides the necessary evidence as requested by the Examiner." Applicant finally argues that the Kapundu' reference directed to compound identification necessitating a hydrolysis step. In conclusion, Applicant argues that it is unclear as to how the examiner establishes an argument based on inherency: "Based on these unobvious distinctions between the applicants' invention and the Kapundu, et al., reference, it is unclear how the examiner establishes an argument for inherency.

The Examiner has carefully considered Applicant's position that the Kapundu' reference fails to teach the instantly claimed invention and Applicant's reasoning for the distinction between what is disclosed by Applicant and what is taught by the prior art reference. However, Applicant's arguments are still not persuasive because Kapundu clearly teaches a methanol extract from powdered seeds of *Napoleonaea imperialis*, on page 615, Column 2, lines 11-12. Furthermore, Kapundu expressly teaches that the methanolic powdered seed extract of the claim-designated plant comprises saponin. For instance, on page 615, last line bridging page 616, line 1, Kapundu clearly teaches extracting the seeds of *Napoleonaea imperialis* with methanol and adding water to the methanolic extract to precipitate a saponin, which is separated by filtration. While Kapundu does teach identification of compounds contained therein the methanolic seed extract, thus necessitating a hydrolysis step of the extract, such disclosure by Kapundu does not negate the fact that Kapundu expressly teaches a methanolic extract obtained from powdered seeds of the claim-designated plant containing a saponin fraction therein. Therefore, while Kapundu does not expressly teach that the prior art methanolic plant extract has biological activity *per se*, biological activity is inherent to

the extract taught by Kapundu because the source of the plant, the particular plant material from the source plant, and the solvent used in the making of the plant extract taught by Kapundu are one and the same as instantly claimed by Applicant. Therefore, antileishmanial activity extract of the methanolic extract of powdered seeds of *Napoleonaea imperialis* taught by Kapundu is inherent to the referenced extract, absent evidence to the contrary.

In the 1.132 Rule Declaration, Dr. Okunji argues that neither Ekpendu (see following rejection) nor Kapundu screened for biological or pharmacological activities of the constituents of claim-designated plant. In this regard, Dr. Okunji states, "Also both groups used similar methods in their chemical investigation of the major constituents of *N. imperialis* known as saponins. In all, both referenced papers the saponins were first hydrolyzed before isolation and chemical identification of the constituents." Unlike Applicant, Dr. Okunji argues that both Ekpendu and Kapundu worked on the hydrolyzed products of *N. imperialis*. For instance, Dr. Okunji explains that he explored the pharmacological activity of naturally occurring compounds rather than hydrolyzed products, which lead to the isolation of naturally occurring saponins contained in *N. imperialis*. The Office appreciates Dr. Okunji discussion of the distribution, isolation and identification of saponins in plants.

Dr. Okunji's arguments have been fully considered. However, they are not found persuasive because Kapundu expressly teaches a methanol extract of powdered seeds of *N. imperialis* comprising saponin. Given that the methanol extract comprised saponins that were not hydrolyzed, Kapundu teaches a non-hydrolyzed extract from

powdered seeds of *N. imperialis*. And for the reasons clearly set forth above, the extract taught by Kapundu inherently deters leishmanial activity.

Applicant is invited to review the following:

"[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). See also MPEP § 2112.01 with regard to inherency and product-by-process claims.

The reference anticipates the claimed subject matter.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele Flood whose telephone number is 571-272-0964. The examiner can normally be reached on 7:00 am - 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on 571-272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MICHELE FLOOD
PRIMARY EXAMINER

Michele Flood
Primary Examiner
Art Unit 1655

MCF
May 28, 2007

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

APPLICANT: Okunji, et al.	DATE: November 30, 2007
SERIAL NO.: 09/428,203	GAU: 1655
FILED: October 17, 1999	EXAMINER: M. Flood

FOR: PLANT DERIVED ANTI-PARASITIC AND ANTI-FUNGAL COMPOUNDS AND METHODS FOR EXTRACTING THE COMPOUNDS

AMENDMENT AND RESPONSE

Dear Sir,

The following is an amendment and response to the Examiner's Office Action dated May 30, 2007. This response is timely filed within the six month period of response. A three month extension of time is respectfully requested.

The Commissioner is hereby authorized to charge all fees pertaining to the filing of the Request for Continued Examination, a three month extension of time, and any other fees due in connection with the filing of this paper, or credit any overpayment, to U.S. Army Medical Research and Materiel Command Deposit Account No. 210380.

The **claims** begin on page 2.

The **response** to the Examiner's Office Action begins on page 10.

Claims:

1.(currently amended) A biologically active extract comprising a fractionation ~~an~~ extract from at least one plant selected from the group consisting of *Aframomum aulocacarpus*, *Aframomum danielli*, *Dracaena arborea*, *Eupatorium odoratum*, *Glossocalyx brevipes* and *Napoleonaea imperialis*, wherein said extract is obtained using an organic solvent, and wherein said biologically active extract ~~deters leishmanial activity~~ is saponin-enriched and exhibits therapeutic anti-leishmanial activity.

2. (withdrawn) A biologically active extract according to claim 1, wherein said extract is from *Aframomum aulocacarpus*.

3. (withdrawn) A biologically active extract according to claim 2, wherein said extract comprises a Labda-8(17), 12 diene-15,16-dial compound.

4. (withdrawn) A biologically active extract according to claim 1, wherein said extract is from *Aframomum daneilli*.

5. (withdrawn) A biologically active extract according to claim 4, wherein said extract comprises a Labda-8(17), 12 diene-15,16-dial compound.

6. (withdrawn) A biologically active extract according to claim 1, wherein said extract is from *Dracaena arborea*.

7. (withdrawn) A biologically active extract according to claim 6, wherein said extract comprises *Mannispirostan A*.

8. (withdrawn) A biologically active extract according to claim 1, wherein said extract is from *Eupatorium odoratum*.

9. (withdrawn) A biologically active extract according to claim 8, wherein said extract comprises Sakuranetin.

10. (withdrawn) A biologically active extract according to claim 1, wherein said extract is from *Glossocalyx brevipes*.

11. (currently amended) A biologically active extract according to claim 1, wherein said extract is ~~a non-hydrolyzed extract from powdered seeds of *Napoleonaea imperialis*~~ obtained directly from solvent extraction of powdered seeds of *Napoleonaea imperialis* utilizing said solvent.

12. (original) A biologically active extract according to claim 1, wherein said extract is from at least one of roots, stem bark, leaves, fruits or seeds from said plant.

13. (withdrawn) A method of preparing a biologically active extract from at least one plant selected from the group consisting of *Aframomum aulocacarpus*, *Aframomum daneilli*, *Dracaena arborea*, *Eupatorium odoratum*, *Glossocalyx brevipes* and *Napoleonaea imperialis*, the method comprising:

selecting a solvent which dissolves or solubilizes a desired biologically active compound from said plant'

combining said solvent and said pulverized plant to extract said desired biologically active compound; and

removing said solvent from said extract of said desired biologically active compound.

14. (withdrawn) A method according to claim 13, wherein said plant comprises *Aframomum aulocacarpus*.

15. (withdrawn) A method according to claim 13, wherein said plant comprises *Aframomum daneilli*.

16. (withdrawn) A method according to claim 13, wherein said plant comprises *Dracaena arborea*.

17. (withdrawn) A method according to claim 13, wherein said plant comprises *Eupatorium odoratum*.

18. (withdrawn) A method according to claim 13, wherein said plant comprises *Glossocalyx brevipes*.

19. (withdrawn) A method according to claim 13, wherein said plant comprises *Napoleonaea imperialis*.

20 (withdrawn) A topical composition comprising a biologically active extract from at least one plant selected from the group consisting of *Aframomum aulocacarpus*, *Aframomum daneilli*, *Dracaena arborea*, *Eupatorium odoratum*, *Glossocalyx brevipes* and *Napoleonaea imperialis* in a topical carrier.

21. (withdrawn) An oral composition comprising a biologically active extract from at least one plant selected from the group consisting of *Aframomum aulocacarpus*, *Aframomum daneilli*, *Dracaena arborea*, *Eupatorium odoratum*, *Glossocalyx brevipes* and *Napoleonaea imperialis* in an oral carrier.

22. (withdrawn) An intravenous composition comprising a biologically active extract from at least one plant selected

from the group consisting of *Aframomum aulocacarpus*, *Aframomum daneilli*, *Dracaena arborea*, *Eupatorium odoratum*, *Glossocalyx brevipes* and *Napoleonaea imperialis* in an intravenous carrier.

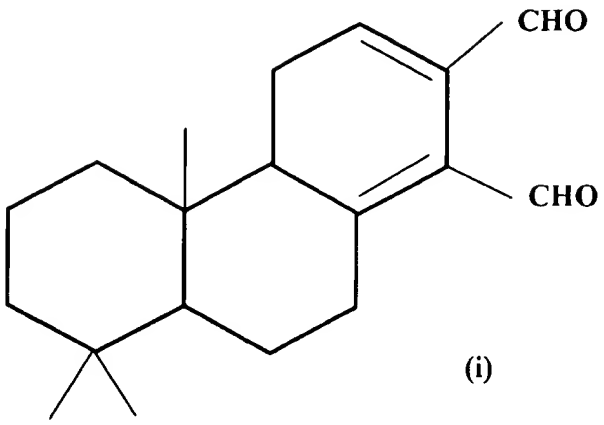
23. (withdrawn) A method of treating a fungal or protozoal disease in a mammal comprising applying a biologically active extract from at least one plant selected from the group consisting of *Aframomum aulocacarpus*, *Aframomum daneilli*, *Dracaena arborea*, *Eupatorium odoratum*, *Glossocalyx brevipes* and *Napoleonaea imperialis*.

24. (withdrawn) Method according to claim 23, comprising applying a topical composition containing said biologically active extract.

25. (withdrawn) Method according to claim 23, comprising ingesting an oral composition containing said biologically active extract.

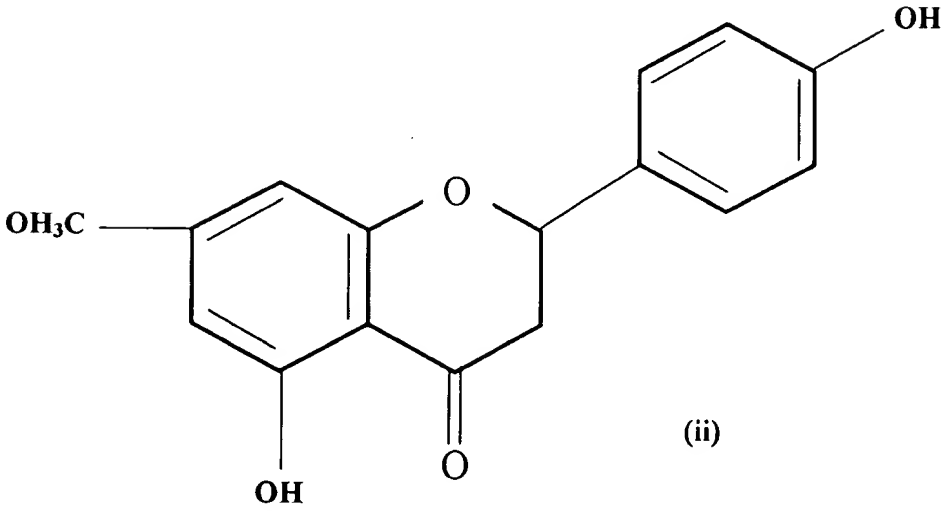
26. (withdrawn) Method according to claim 23, comprising injecting an intravenous composition containing said biologically active extract.

27. (withdrawn) A compound comprising:



(i)

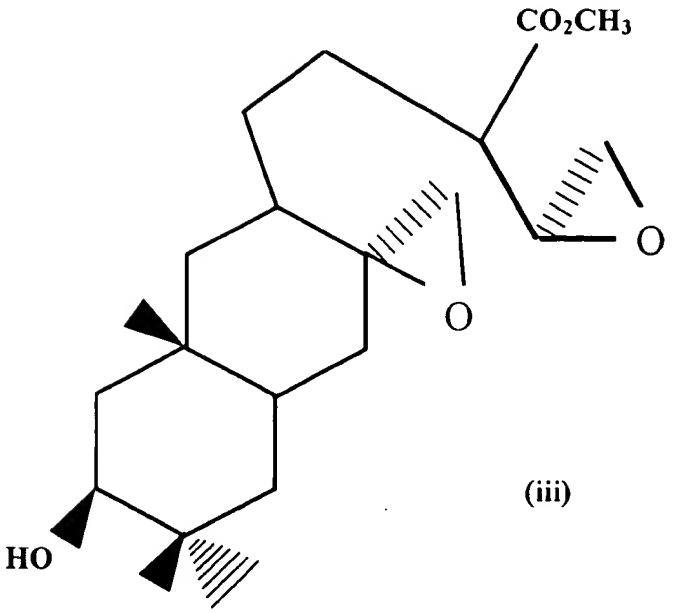
28. (withdrawn) A compound comprising:



(ii)

C71.3%H6.3%O22.4%

29. (withdrawn) A compound comprising:



(iii)

30. (currently amended) A biologically active extract according to claim 1, wherein said solvent is selected from a group consisting of hexane, chloroform, ethyl acetate and methanol wherein said extract is obtained directly from solvent extraction of powdered seeds of said plant utilizing said solvent ~~and said extract is a non-hydrolyzed extract~~ .

31. (previously amended) A biologically active extract according to claim 30, wherein said solvent is methanol.

32. (withdrawn) A biologically active extract according to claim 30, wherein said solvent is ethyl acetate.

33. (withdrawn) A method for forming a biological extract of *Napoleonaea imperialis* including the steps of:

(a) mixing powdered seeds of *Napoleonaea imperialis* with a solvent;

(b) extracting said extract from said seeds; and

(c) concentrating said extract to dryness.

34. (withdrawn) A method for forming a biological extract as recited in claim 33 wherein said solvent of said mixing step (a) is methanol.

35. (withdrawn) A method for forming a biological extract ass recited in claim 33, wherein said solvent of said mixing step (a) is ethyl acetate.

36. (cancelled).

37. (cancelled).

38. (previously amended) A biologically active extract according to claim 11, wherein said solvent is methanol.

39. (cancelled).

40. (cancelled).

Response:

(1) Applicants acknowledge Examiner's withdrawal of the rejection of the claims as being anticipated by Ekpendu, et al.

(2) Applicants acknowledge the Examiner's holding of the restriction requirement as final. Applicants continue to assert that the restriction is improper for the reasons stated in Applicants' response of April 12, 2007. Applicants also assert their right to file a divisional application directed to all restricted claims.

(3) Applicants acknowledge the Examiner's rejection of claims 11, 20, 31, 38 and 40 under 35 U.S.C. §112, first paragraph. The Examiner asserts that the recitation of "a non-hydrolyzed extract" in claims 11 and 30 lack antecedent basis and constitute new matter. Applicants respectfully and strongly disagree with the Examiner's position that "there is not sufficient support for the new aforementioned genera/genus to preclude compositions that are not a "non-hydrolyzed extract." The specification is explicit in its disclosure of the Material and Methods, Preparation of Test Materials, Antifungal tests, In vitro Antileishmanial Activity, the strains of Leishmania tested, the RAM Drug Test Procedure, the Bioassay-directed fractionation of Napoleonaea imperialis, et al. *See*

specification, pages 9+. There is no disclosure of any hydrolysis step to obtain the extract per the present invention. Thus, the Examiner's position that the explicit omission of "non-hydrolyzed extract" infers "hydrolyzed extract" is incorrect.

If one were to consider the Examiner's position to its fullest extent, the "hydrolyzed extract" would also have to have been explicitly stated. The Applicants' omission of "hydrolyzed extract" is intentional, as the invention is not directed to hydrolysis. The reasons for the lack of a hydrolysis step are further discussed in Dr. Okunji's Rule 132 affidavit submitted December 20, 2006. *See* page 7, lines 6+ of the affidavit. In view of the specification and the affidavit, it is clear that Applicants do not disclose hydrolysis of the extract. The present amendment to the claims further clarifies the subject matter of the present invention. Support for the amendment to claim 1 can be found on pages 10-11, page 15, line 11+, and page 17, lines 20+ of the specification. Support for the amendment to claim 11 and 30 can be found on page 15, line 5+. Claim 40 has been cancelled.

(4) Claims 1, 11, 12, 30, 31, 38 and 40 were rejected as being anticipated by Kapundu et al.

The Examiner asserts that the Rule 132 affidavit submitted by Dr. Okunji was considered and not found persuasive. The Examiner states that the Applicants' arguments were unpersuasive for the following reasons:

(a) "Kapundu clearly teaches a methanol extract from powdered seeds of Napoleonaea imperialis;"

(b) "Kapundu expressly teaches that the methanolic powdered seed extract of the claim designated plant comprises saponin;"

(c) "While Kapundu does teach identification of compounds contained therein the methanolic seed extract, thus necessitating a hydrolysis step of the extract, such disclosure by Kapundu does not negate the fact that Kapundu expressly teaches a methanolic extract obtained from powdered seeds of the claim-designated plant containing a saponin fraction therein;"

(d) "Kapundu does not expressly teach that the prior art methanolic plant extract has biological activity per se, biological activity is inherent to the extract taught by Kapundu because the source of the plant, the particular plant material from the source plant, and the solvent used in the making of the plant extract taught by Kapundu are one and the same as….claimed by Applicant;" and

(e) "antileishmanial activity extract of the methanolic extract of powdered seeds of Napoleonaea imperialis taught by

Kapundu is inherent to the referenced extract, absent evidence to the contrary.

The Examiner's rejection is respectfully traversed. The Examiner's positions designated as (a), (b) and (c) above indicate reasoning based on the narrow interpretation of product-by-process claims. *In re Thorpe,* 777 F.2d 695 (Fed. Cir. 1985), defines the need for product-by-process claims "to enable an Applicant to claim an otherwise patentable product that resists definition by other than the process by which it is made. For this reason, even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself." *See Thorpe* at 9. Thus, it is the Examiner's position that, even though Kapundu, et al's, methodology is distinguished from that of the present invention, the similarity of an intermediate step of Kapundu, et al., to the final step of the present invention are sufficient grounds to establish that the isolate taught by Kapundu, et al., anticipate the extract recited in the present claims.

The Examiner is in error on two grounds. Firstly, no product-by-process claims are recited in the present application. The steps by which the present are patentably novel and unobvious, and the extract produced therefrom, are biologically active, therapeutic compounds that have been shown to have efficacy against leishmania. The specification of the

present invention is very explicit in its disclosure of the process by which the extract of the present invention is obtained. Furthermore, the specification is equally explicit in the compounds that are extracted and their efficacies. No such disclosure is made by Kapundu, et al. To reiterate, Applicants' Rule 132 affidavit states that the adopted hydrolysis of Kapundu, et al., incurs "significant concerns such as artifacts formation, not being able to obtain genuine aglycone, possibility of epimerization transformation, etc." *See* page 7 of the affidavit. These concerns cannot be dismissed as "obvious" or "anticipated" as they impact the very bio and therapeutic activity sought by the present application.

Secondly, the 132 affidavit provided by Dr. Okunji very specifically states that "investigators were chemists and therefore more interested on the chemistry of this plant rather than their biological or therapeutic properties. Secondly. . . Kapundu [did not] screen[] for biological or pharmacological activities of the constituents of this plant. . . . It is remarkable to note that [Kapundu] worked on the hydrolyzed products instead of the intact plant constituents (saponins)" *See* 132 Affidavit, page 3-4. Thus, Kapundu, et al., may obtain an intermediate solvent extract, but it is not directed to utilizing the extract in the manner of the present claims. This is a patentable distinction, as the methodology in Kapundu, et

al., cannot lead to the same isolate as the present invention, and the difference in the Kapundu, et al., methodology is patentably distinct from that of the present invention. Thus, mere mention of a common step cannot anticipate the present claims if the products obtained therefrom are distinct.

With respect to arguments (d) and (e) above, Applicants respectfully traverse the Examiner's position. Examiner has failed to prove her burden that Kapundu, et al., anticipate the present claims by inherently teaching biological activity and antileishmanial activity. Kapundu, et al., do not disclose any biological activity, let alone activity against leishmania. It is the Applicants who disclose biologic activity and specific efficacies against leishmania. Thus, the Examiner is utilizing the Applicants' own disclosure to support her rejection of the claims. The Examiner is no doubt aware that, in the absence the admission by Applicants that the matter disclosed in the specification is prior art, such a rejection is impermissible.

(5) The Examiner also states that the Rule 132 affidavit is unpersuasive. The Examiner states that "The Office appreciates Dr Okunji's discussion of the distribution, isolation and identification of saponins in plants." However, the Examiner provides no statements or assertions as to why Dr Okunji's statements are unpersuasive. A mere statement that an affidavit

is unpersuasive is insufficient to meet the Examiner's burden. Dr. Okunji's statements have direct bearing on the scope of the work and state of the prior art at the time of the present invention. It is particularly relevant that the Kapundu group were not considering biological or therapeutic activity. In the absence of this significant factor, Kapundu, et al., cannot have anticipated the present invention. The Examiner's statement that a partial process for the isolates disclosed by Kapundu, et al., provides sufficient anticipatory evidence of biological and therapeutic activity in the extract claimed by the Applicants is contradictory to the substantive discourse of the patentably distinguishable features of the present invention.

Furthermore, Dr. Okunji is a leading pharmocognosist. His affidavit provides an extensive and in-depth analysis of saponin extraction, the relevance of source in the extraction process and the problems associated with hydrolysis as disclosed by Kapundu, et al. These distinctions provide substantive supportive evidence of the unanticipated and unobvious claimed subject matter of the present invention. Applicants strongly disagree with the Examiner's dismissive stance with respect to the significance of the affidavit and its relevance to the Kapundu, et al., reference. Applicants respectfully request that this evidence be given its full force.

To that end, it is the Applicants' position that the Examiner has not met her burden in her holding of the claims of the present invention as being anticipated by Kapundu, et al. Therefore, Applicants respectfully request that the rejection of the claims be withdrawn and the application be put in condition for allowance.

The Examiner is respectfully requested to send all correspondences to: Elizabeth, Arwine, Esq.; Office of the Staff Judge Advocate; U.S. Army Medical Research & Materiel Command; 504 Scott Street, Fort Detrick, Maryland 21702-5012; Attn: MCMR-JA (Ms. Arwine).

Please direct any questions regarding this case to Ms. Abanti Bhattacharyya, Esq. at (410) 964-9553.

11-30-07
Date

Abanti Bhattacharyya, Esq.
Reg. No. 36,681

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BIOLOGICAL ACTIVITY OF SAPONINS FROM TWO *DRACAENA* SPECIES

C.O. Okunji[1,2], M.M. Iwu, J.E. Jackson, and J.D. Tally

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Washington DC 20307-5100
[2]NRC Senior Research Associate; on leave of absence
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ABSTRACT

Many species of the west African "soap tree" *Dracaena* are used in traditional medicine for the treatment of a variety of diseases. In continuation of our search for anti-infective agents from plants implicated in traditional medicine, we evaluated the biological activities of saponins from extracts of *Dracaena mannii* and *Dracaena arborea* by using a battery of test systems such as radiorespirometry, Cytosensor®, bioautography, and agar dilution methods and molluscicidal tests.

Bioassay-directed fractionation of the methanol extracts of seed pulp using a combination of chromatographic techniques, gel filtration, droplet countercurrent chromatography (DCCC), and low-pressure liquid chromatography (Lobar), led to the isolation and characterization of spiroconazole A, a pennogenin triglycoside [3β-*O*-{(α-L-rhamnopyranosyl(1→2),α-L-rhamnopyranosyl(1→3)-β-D-glucopyranosyl}-17α-hydroxyl-spirost-5-ene] (Fig. 1). As the active constituent, spiroconazole A exhibited pronounced antileishmanial, antimalarial, and molluscicidal activities. This paper also reports on the fungistatic, fungicidal and bacteriostatic activity of spiroconazole A against 17 species of fungi and 4 of bacteria.

INTRODUCTION

Available drugs for the treatment of diseases due to various protozoal infections are inadequate due to increasing parasite resistance and serious toxicity associated with some of them. In continuation of our screening program in search of anti-infective agents from plants implicated in traditional medicine, we evaluated the biological activities of saponins from extracts of *Dracaena mannii* and *D. arborea* using a battery of test systems (such as radiorespirometry, Cytosensor®, bioautography, and agar dilution methods, and

Saponins Used in Traditional and Modern Medicine
Edited by Waller and Yamasaki, Plenum Press, New York, 1996

molluscicidal tests). The initial goal of this program was the identification of compounds having antifungal and molluscicidal properties. Previously, we reported one antifungal and several molluscicidal constituents of *D. mannii* (Okunji *et al.*, 1990, 1991).

Because antiprotozoal and antifungal activities are frequently associated with the same or chemically similar compounds, we considered it probable that spiroconazoles, the main saponin constituent of the two species of *Nigerian Dracaena*, would have antiprotozoal activity.

In general, antiprotozoals are not given high priority for commercial development because the per capita health expenditure in many tropical countries is less than the cost of one course of drug therapy. Thus, many "modern" antiparasitic drugs were initially marketed >40 years ago. Clinical intervention in the treatment of leishmaniasis, for example, is presently limited to the use of pentavalent antimonials (SbV), sodium stilbogluconate and *N*-methylglucamine antimonate, and secondarily, amphotericin B, or pentamidine (Croft, 1988; Bryceson, 1987). Treatment with these agents is not consistently effective, particularly for the most virulent leishmanial disease forms (Croft, 1988; Bryceson, 1987; Jha, 1983; Rocha *et al.*, 1980; Mebrahtu *et al.*, 1989). Furthermore, most of the current antiprotozoal drugs are very toxic. It would, therefore, be useful to develop more effective, less toxic, and orally active antileishmanials. The antileishmanial activity of the extracts from the Nigerian plant *Dracaena mannii* has been evaluated by determining their effect on parasite growth and on the catabolism of various substrates using the radiorespirometric microtest, RAM. The *in vitro* RAM, a metabolic test using leishmanial promastigotes (i.e. the monoflagellate extracellular culture forms shown in Fig. 2a), had been developed earlier in our laboratories. The RAM relies on drug inhibition of parasite production of $^{14}CO_2$ from a battery of ^{14}C-substrates to detect drug-mediated parasite damage at low drug concentration within a short time (Jackson *et al.*, 1989, 1990).

Another protozoan disease, malaria, remains the greatest human killer among parasitic infections, despite the world-wide effort to combat the disease and attempts at the eradication of the causative organisms. The emergence of multi-drug-resistant strains of *Plasmodium falciparum*, the most lethal of the malaria parasites, poses a serious health-care problem, not only in the malaria-endemic countries but also among international travellers.

Protozoan infections are also a major cause of mortality and morbidity in immunosuppressed patients, as in acquired immunodeficiency syndrome (AIDS). A single therapeutic agent active against different types of protozoa would be a major innovation in the treatment of these diseases.

Similarly, fungal and yeast infections are becoming increasingly resistant to modern drugs. In immunologically compromised individuals, for example, complications arising from uncontrollable fungal infections are among the leading cause of death. There is, therefore, a need for new and effective alternative treatment. This paper describes and summarizes our investigation of the therapeutic potential of these commonly used medicinal plants using a battery of biologic test systems.

MATERIALS AND METHODS

Plant Materials

Two species of *Dracaena*, *D. mannii* and *D. arborea*, were collected at Isi-elu, near the Nsukka campus of the University of Nigeria in February, 1985. The collection was chosen from plants listed in an ethnomedicinal survey carried out among the Igbo people (Iwu, 1981/82, 1993). The *Dracaena* spp. plants were taxonomically identified by Mr. A. Ozioko of the Department of Botany, University of Nigeria, Nsukka and the identities confirmed by Dr. J. C. Okafor of the Forestry Herbarium, Enugu. Voucher specimens

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Extraction and Isolatio

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D. arborea.

Antimalarial Bioassay

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have been deposited at the Department of Pharmacognosy Herbarium, University of Nigeria, Nsukka. Prior to extraction, the plant material was dried at 40 °C and the dried vegetable drug ground to coarse powder.

For column chromatography (CC), silica gel 60 size 0.063-0.200 mm (70-230 mesh ASTM, EM Science, was used, and Sephadex LH-20, Sigma, for gel filtration. Low-pressure liquid chromatography (Lobar) was done using a LichroPrep RP-8 column (40-63 mm 2.5 X 25 Merck) equipped with an FMI pump. DCCC equipment consisted of type 300 glass tubes (length 400 mm, I.D. 2 mm) (Tokyo Rikakikai, Nishikawa Bldg, Toyama-Cho, Kanda Chiyoda, Tokyo), solvent system: $CHCl_3$:MeOH:H_2O (7:13:8). The solvent systems for CC were all homogeneous. Thin-layer chromatography (TLC) was used on the Analtech normal phase 10 x 20 cm plates. The TLC plates were developed using solvent systems were: I. $CHCl_3$:MeOH:H_2O (65:40:5), and II. $CHCl_3$:MeOH:H_2O (40:10:1). Sephadex LH-20 gel (25-100 mm size; Sigma) filtration was performed using methanol as eluant.

Extraction and Isolation Protocol

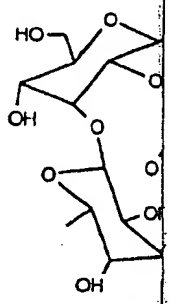
The powdered fruit pulp of the two species of *Dracaena* was Soxhlet-extracted with solvents of increasing order of polarity in two batches, starting with petroleum ether (bp 40-60 °C) (48 h), chloroform (48 h), ethyl acetate (48 h) and methanol (48 h). Each extract was concentrated to dryness *in vacuo* using a rotary evaporator at 40 °C. The isolation and purification of spiroconazole A, B, and C from *D. mannii* have been described elsewhere (Okunji *et al.*, 1991). Briefly, a portion of the methanol extract (20 g) was first partitioned between chloroform-methanol-water mixture (2:2:1) to yield a saponin-enriched lower organic layer which was concentrated to dryness *in vacuo* and lyophilized. Five grams of the active milky-colored fraction were dissolved in a minimum volume of methanol and chromatographed on a Sephadex LH-20 column (2.0 X 50 cm) with methanol as eluant. The flow rate was adjusted to 2.5 ml min-1 and 10-ml fractions were collected. One gram of the crude active saponin fraction was dissolved in 10 ml of a (1:1) mixture of both upper and lower phases of the solvent system chloroform-methanol-water (7:13:8) and then subjected to droplet countercurrent chromatography (DCCC) in the ascending mode. The more polar upper layer was used as the mobile phase. The sample was injected into the apparatus via a 15-ml sample chamber. The flow rate was 10 ml h-1, and the eluates were collected in 5-ml fractions. The monitoring of the fractions was carried out with TLC aluminum sheet silica gel 60-F254 in solvent systems I and II. The saponins were detected with Godin reagent (Godin, 1954). Low-pressure liquid chromatography on a Lichroprep RP-8 (40-63 mm) column was used as the final purification of the saponins. Two molluscicidal spirostanol saponins that we designated as spiroconazole A and B, and a third non-molluscicidal saponin, spiroconazole C, were isolated and characterized on the basis of spectroscopic evidence. Similar phytochemical and biological patterns were observed for *D. arborea*.

Antimalarial Bioassay

The *in vitro* antimalarial assays were performed by using a modification of the semi-automated microdilution technique described earlier (Desjardins *et al.*, 1979, Milhous *et al.*, 1985). Two *Plasmodium falciparum* malaria parasite clones, designated Indochina (W-2) and Sierra Leone (D-6), were utilized in susceptibility testing. The W-2 clone is resistant to chloroquine, pyrimethamine, sulfadoxine, and quinine, and the D-6 clone is resistant to mefloquine. The test compound, spiroconazole A, was dissolved in DMSO and serially diluted using malarial growth medium. Drug-induced reduction in uptake of tritiated hypoxanthine was used as an index of inhibition of parasite growth. In this assay,

Table 1. Antifungal activity of spiroconazole A, compared to current antifungal drugs: miconazole and ketoconazole. Both minimum inhibitory concentration , MIC, and minimum fungicidal concentration (MFC) are given in μg ml^{-1}. Adapted with permission from C.O. Okunji, C.N. Okeke, H.C. Gugnani, and M.M. Iwu, Int. J. Crude Drug Res. 28:193-199, 1990.

	Spiroconazole A		Miconazole		Ketoconazole	
Test Fungi	MIC (μg/ml)	MFC (μg/ml)	MIC (μg/ml)	MFC (μg/ml)	MIC (μg/ml)	MFC (μg/ml)
Dermatophytes						
Trichophyton mentagrophytes	12.50	25.00	6.25	25.00	6.25	25.00
Trichophyton tonsurans	12.50	50.00	1.56	6.25	0.78	3.13
Trichophyton soudanense	6.25	12.50	0.20	0.78	0.05	0.39
Trichophyton rubrum	12.50	25.00	3.13	6.25	1.56	6.25
Microsporum audouinii	12.50	25.00	1.56	3.13	0.20	0.39
Microsporum grpseum	50.00	100.00	12.50	100.00	0.30	1.56
Pathogenic Dermatiaceous Fungi						
Phialophora verrucosa (ATCC 50768)	50.00	100.00	0.05	0.20	0.10	0.20
Fonsecaes pedrosoi (ATCC 52593)	25.00	50.00	0.20	0.39	0.05	0.10
Cladosporium carrionii	12.50	12.50	0.10	0.39	0.10	0.30
Cladosporium tennuisimum (ATCC 623337)	100.00	100.00	0.78	3.13	0.39	0.78
Exophiala jeanselmei (ATCC 62791)	25.00	100.00	0.20	0.39	0.10	0.39
Ramichloridium subulatum (ATCC 62339)	25.00	1001.00	0.39	25.00	0.20	0.39
Yeasts						
Candida albicans	25.00	100.00	6.25	6.25	12.50	25.00
Candida tropicalis	100.00	100.00	6.25	6.25	1.56	1.56
Trichosporon cutaneum	6.25	6.25	0.05	0.02	0.02	0.78
Geotrichum candidum	12.50	12.50	1.56	1.56	0.39	0.78
Rhodotorula sp.	25.00	100.00	1.56	1.56	0.78	1.56



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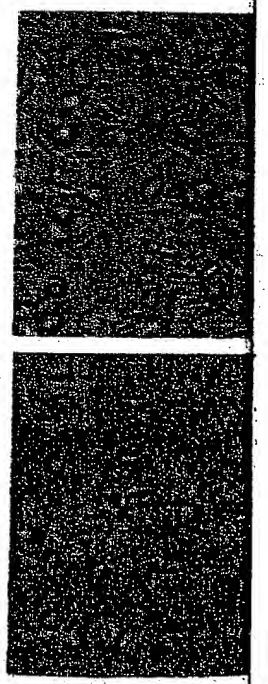

Fig. 2. Photograph sho
DMSO), and spirocon
after 17.5 h drug exposu

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	Ketoconazole	
ıl)	MIC (μg/ml)	MFC (μg/ml)
10	6.25	25.00
5	0.78	3.13
8	0.05	0.39
5	1.56	6.25
3	0.20	0.39
00	0.30	1.56
)	0.10	0.20
)	0.05	0.10
)	0.10	0.30
3	0.39	0.78
)	0.10	0.39
10	0.20	0.39
5	12.50	25.00
5	1.56	1.56
2	0.02	0.78
5	0.39	0.78
5	0.78	1.56

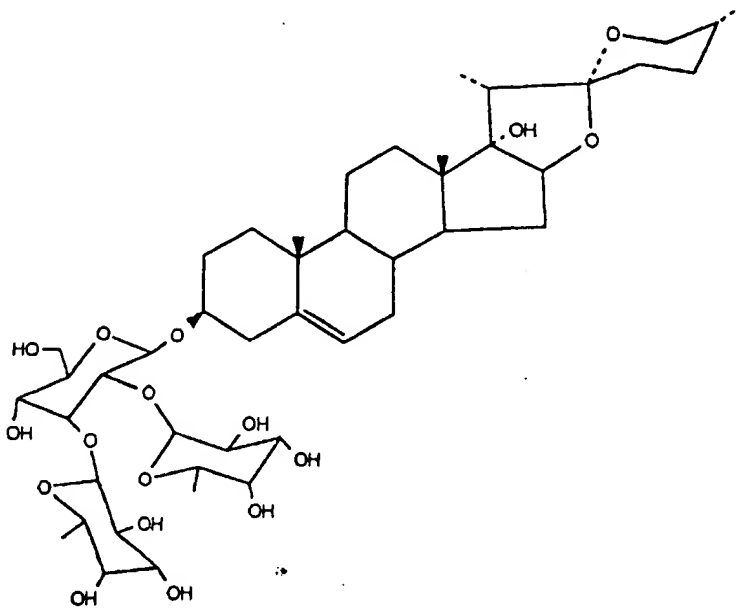

Fig. 1. Chemical structure of spiroconazole A.

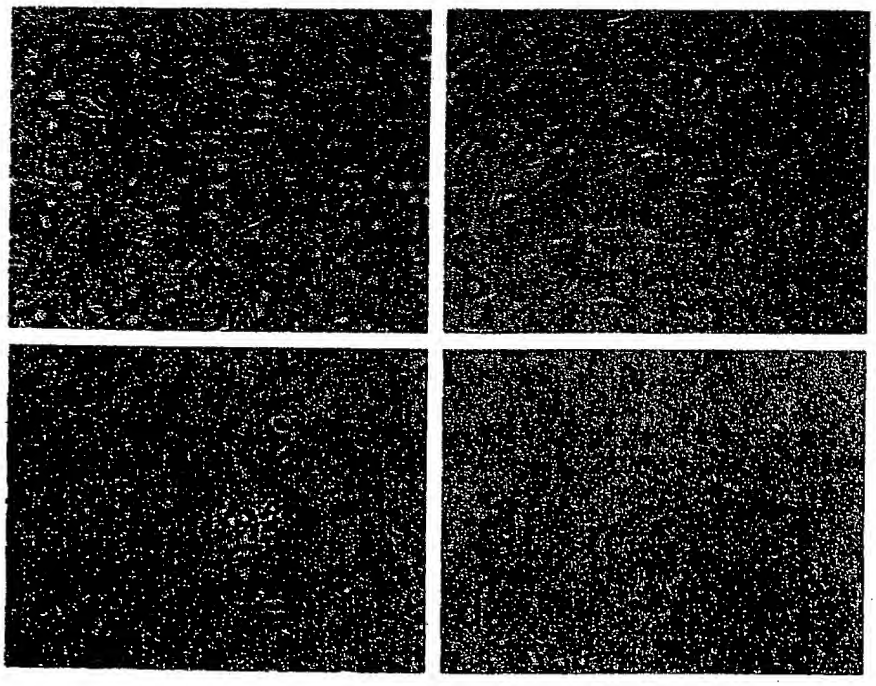

Fig. 2. Photograph showing leishmanial promastigote morphology of control (6a: 0.6% DMSO), and spiroconazole A-treated parasites (6b: 6.3-; 6c: 12.5-, and 6d: 50 μg ml^{-1}) after 17.5 h drug exposure during logarithmic phase growth.

the spiroconazole A treatment resulted in an IC_{50} value of 0.03 μg ml^{-1} for the W-2 clone, and 0.1μg ml^{-1} for the D-6 *Plasmodium falciparum* clone.

Antifungal Tests

TLC Bioassay:

A method similar to that of Homans and Fuchs (1970) was employed in this investigation. This technique involves direct spraying of thin layer chromatograms with conidial suspensions of a test organism. About 100 μg of extract was spotted on silica gel TLC plates and developed with solvent system I. Developed plates were separately sprayed with either a spore suspension of *Cladosporium cucumerinum*, and subsequently with spore suspensions of *Cladosporium carrionii, Cladosporium cladosporioides, Cladosporium tennuisimum* and *Fonsecaea pedrosoi*, to determine the spectrum of activity. The plates were then incubated in sealed humid chambers at room temperature for four days in the dark. Antifungal activity was manifested by the appearance of a white spot, corresponding to the position of the active compound, surrounded by a grey-black fungal growth all over the plates (Fig. 3). Bioassay-directed fractionation of the active extracts using a combination of chromatographic techniques led to the isolation and characterization of the spiroconazole group of compounds. The most active compound, spiroconazole A, gave a clearly visible inhibition zone at a concentration of 5 μg, which is below the limit of the detecting reagent (Godin's spray reagent).

Agar Diffusion Method:

The dermatiaceous fungi used in this work were environmental isolates (Okeke and Gugnani, 1986) and have been deposited in the American Type Culture Collection (ATCC). Culture accession numbers (designated ATCC#) are indicated in Table 1. The yeasts and dermatophytes were clinical isolates from the University of Nigeria Teaching Hospital, Enugu.

The antifungal activity of spiroconazole A was evaluated by the agar diffusion method using Emmon's Sabouraud dextrose agar (ESDA) as the growth medium. Stock solutions of the test compound and reference standard antifungal drugs, ketoconazole (R41,4001; lot C4,701) and miconazole (ZR-14,889; lot H1001), were prepared at initial concentrations of 10 X 10^3 μg ml^{-1} of dimethyl sulfoxide (DMSO). Serial 2-fold concentrations (0.025-100 μg ml^{-1}) were incorporated into the growth medium and plates were poured. ESDA incorporating only DMSO was used as control. Plates were inoculated with 0.05 ml of the fungal suspensions (approximately 10^5 conidia or hyphal elements/ml 0.9% sterile saline) in triplicate and incubated at 30 °C until macroscopically visible growth appeared in the control (48-96 h post incubation). The minimum inhibitory concentration (MIC) was the lowest concentration of compound that inhibited fungal growth. The minimum fungicidal concentration (MFC) was determined by culturing portions of the fungal inocula of the MIC test plates showing no sign of fungal growth onto fresh plates of ESDA in triplicate. The plates were incubated at 30 °C for 48-96 h. The lowest concentration at which the fungal inoculum yielded no visible growth was taken as the MFC.

In this assay, the most active analog, spiroconazole A, was shown effective against the yeasts and fungi at the drug concentrations listed in Table 1.

In Vitro Antileishmanial Activity

An *in vitro* radiorespirometric microtest (RAM) technique was used to evaluate the spiroconazoles for possible antileishmanial activity. This method, as already noted, relies

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Leishmania species/str

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activities as close to 40 mCi
The quantitative promastig
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RAM Drug Test Proced

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on drug inhibition of parasite production of $^{14}CO_2$ from a battery of ^{14}C-substrates by promastigotes to detect drug-mediated parasite damage at low drug concentration within a short time. The test is quantitative, rapid, consistent, and is conducted in serum-free medium in which prior adaptation is not necessary to cultivate the so-called "difficult to grow" species.

Leishmania species/strains:

A clinical isolate of visceral *Leishmania (Leishmania) chagasi*, MHOM/BR/84/BA-13, was used for this study. This isolate was selected because sensitivity to SbV was previously determined using RAM. MHOM/BR/84/BA-13 is sensitive to Pentostam®, sodium antimony gluconate, at 6 μ ml^{-1} Sb (20 μg ml^{-1} drug); and to Glucantime®, *N*-methylglucamine antimonate, at 80 μg ml^{-1} Sb (286 μg ml^{-1}drug).

The ^{14}C-labelled substrates are (numerical codes given in the x-axis of Fig. 4) ^{14}C-substrates: (3) L-aspartic acid (4-^{14}C); (7) glycine (U-^{14}C); (10) L-leucine (1-^{14}C); (13) L-ornithine (1-^{14}C); (25) D-galactose (1-^{14}C); (28) D-mannose (1-^{14}C); (44) succinic acid (1,4-^{14}C); and (46) Na-butyrate (1-^{14}C). All ^{14}C-substrates were selected with specific activities as close to 40 mCi mM^{-1} per carbon atom as obtainable from commercial sources. The quantitative promastigote growth inhibition assay was used as a guide to identify isolates exhibiting antileishmanial activity.

RAM Drug Test Procedure:

The procedure was conducted as previously described (Jackson *et al.*, 1989, 1990). Promastigotes were maintained in log phase growth for 3 successive transfers (48-72 h apart) prior to radiorespirometric (RAM) testing. Test samples (or PBSS, 0.1 M phosphate-buffered balanced salt solution, plus drug solvent, DMSO, for parallel control cultures) was added 24 h after the third promastigote transfer to fresh growth medium. Incubation in the presence of plant samples was continued for 96 additional hours while the parasites remained in mid-log phase growth. The test compound was tested at 50 μg ml^{-1}. Drug sensitivity or resistance was based on ^{14}C-substrate(s) (listed above) for which $^{14}CO_2$ release was decreased for drug-treated parasites compared to parallel tests of phosphate-buffered balanced salt solution and vehicle (PBSS+DMSO) controls. Each experiment consisted of parallel: (a) duplicate tests of drug-treated parasites; plus (b) duplicate tests of drug vehicle control-treated parasites; plus (c) one "nonbiological" sterility control. The nonbiological control consisted of each ^{14}C-substrate (one substrate per microtiter tray well), and PBSS (the same PBSS batch used to wash, to suspend the parasites, and to make drug solution). Since there were no parasites in the nonbiological control, any $^{14}CO_2$ detected was attributed either to biologic contamination (or, less likely, chemical contamination) of the ^{14}C-substrates resulting in breakdown of such substrates. If radioactivity above background (10 dpm) was detected in the nonbiological control, the suspect solution(s) was replaced and the experiment was repeated.

The results (Fig. 5) show that spiroconazole A strongly inhibited the growth of the *Leishmania* strains at the dose of 50 μg ml^{-1}. This test compound also significantly inhibited the leishmanial catabolism of various ^{14}C-substrates, resulting in a maximum suppression of more than 95% when compared with the values observed for the controls (Fig. 4).

Antifungal Activity of *Dracaena mannii*
Fruit Pulp Against
Cladosporium cucumerinum

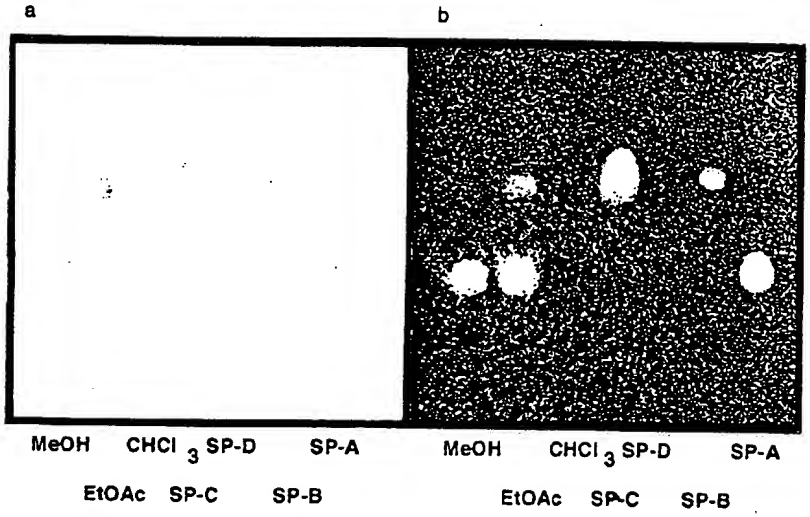


Fig 3. Thin layer chromatography (TLC)-bioassay on a silica gel plate, showing inhibition of the fungus, *Cladosporium cucumerinum*, by *Dracaena mannii* extracts and isolated compounds.

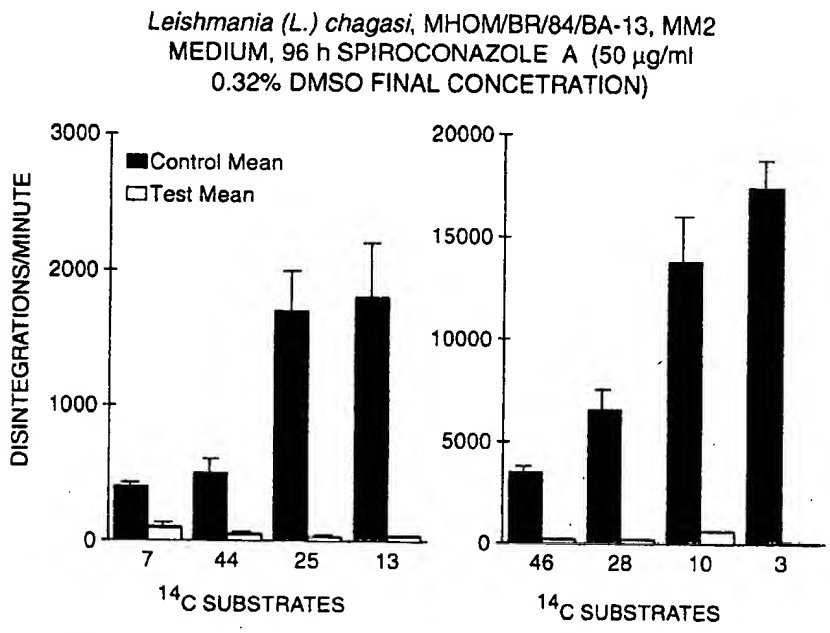
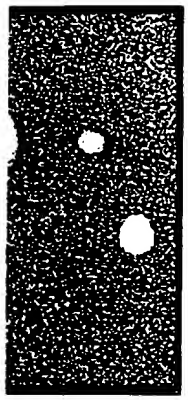


Fig. 4. Radiorespirometric (RAM) data showing markedly reduced respiration of *Leishmania (Leishmania)* chagasi, a visceral disease parasite after spiroconazole A treatment *in vitro*. The vehicle-control-treated parasite respiration is represented by the light grey vertical bars; the spiroconazole A (50 µg ml^{-1} for 96 h)-treated parasites, by the solid black bars. The ^{14}C-substrate numeric codes (x-axis) were given in the corresponding section of the Materials and Methods.



SP-D SP-A

C SP-B

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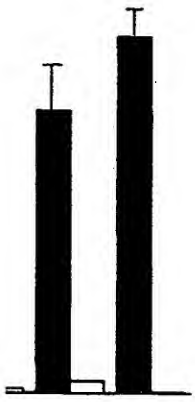

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Cytosensor Microphysiometer System

The rate at which cell excrete acids into their environment is closely linked to the rate which they convert food to energy, i.e their metabolic rate. The Cytosensor Microphysiometer System (CMS) measures the rate at which cells acidify their immediate environment. The CMS monitors these metabolic changes as changes in the rate of cellular acidification. In this way, the system provides a real-time, noninvasive means of measuring cellular responses to a wide variety of agents (McConnell *et al.*, 1992).

Spiroconazole A was tested for antileishmanial activity *in vitro* using CMS. Promastigote leishmanial forms were exposed to spiroconazole A in the chemically defined, serum-free medium (Jackson *et al.*, 1989) for 17.5 h during logarithmic growth phase. To prepare cells for CMS, the nonadherent cell protocol was utilized. Briefly, the cells were centrifugally concentrated, counted by hemacytometer, and resuspended in 0.2% low-temperature agarose in balanced salt solution. Leishmanial promastigotes, a 10-µl suspension containing 1-2 X 10^6 cells in agarose, were placed in each of 8 Cytosensor flow-chambers and the low-buffer formulation of RPMI medium (pH 7.4, Molecular Devices Corporation) was pumped over the cells. The repetitive pump cycle time was 2.0 min (88 sec of medium flow followed by 32 sec of pump off). During the 32 sec the peristaltic pump was not operating, the rate of leishmanial acidification of RPMI medium in each of 8 separate cell chambers was measured. Acidification rates during the two-min cycle resulted in less than 0.1 pH unit change and were not detrimental to the leishmanial cells. The CMS leishmanial acidification rates (representative data given in Fig. 6) were relatively constant for each drug treatment concentration (6.3, 12.5, 50 µg ml^{-1}) and vehicle control (0.6% DMSO) duplicate pair, tested in parallel simultaneously, over the 11-h observation period.

In Vivo Antileishmanial Activity

The *in vivo* antileishmanial activity was determined by administering various doses of the spiroconazole A to golden hamsters and determining the effect on laboratory-induced visceral and cutaneous leishmaniasis of the animals. For this assay, the compounds were tested against *Leishmania (Leishmania) donovani*, MHOM/SD/43/Khartoum, a causative organism of kala azar or visceral leishmaniasis, and *Leishmania (Viannia) panamensis*, MHOM/PA/83/WR539, an etiological agent of simple cutaneous leishmaniasis. Spiroconazole A was tested in each *in vivo* leishmanial model by the oral, intramuscular, and subcutaneous routes of administration.

The results of the activity of the spiroconazole A administered through the intramuscular route to hamsters infected with cutaneous *L. panamensis* represent an example of dose-dependent *in vivo* activity of the compound. At a dose of 104 mg kg^{-1} total dose (equivalent to 26 mg kg^{-1} per day) of the spiroconazole A, administered by intramuscular route twice a day for 4 days, the test substance produced a 73% inhibition of lesion caused by *L. panamensis* in hamsters. A dose of 52 mg kg^{-1} (13 mg kg^{-1} per day) by the same regimen gave a 51% reduction of the lesion area, and at a dose of 13 mg kg^{-1} (3.25 mg kg^{-1} per day) 7% reduction of the lesion area was observed.

Antibacterial Activity:

Antibacterial activity of spiroconazole A was evaluated by the agar well assay method using trypticase soy agar (Difco) as the growth medium. Plates of this medium were inoculated with 0.1 ml of a 6th culture of the test isolate in trypticase soy broth, a sterile glass spreader being used to ensure uniform growth of the inoculum. Wells (10 mm diameter) were made in the seeded agar plates and 0.1 ml of 1% solution of spiroconazole

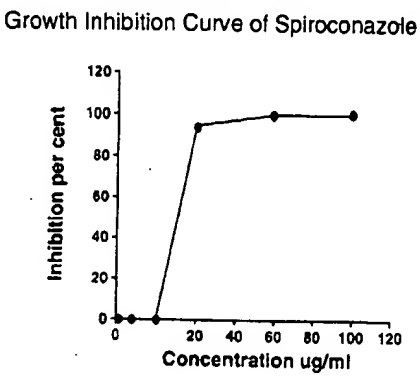

Fig. 5. Growth inhibition (y-axis) for *Leishmania (Leishmania)* chagasi with increasing spiroconazole A concentration (x-axis).

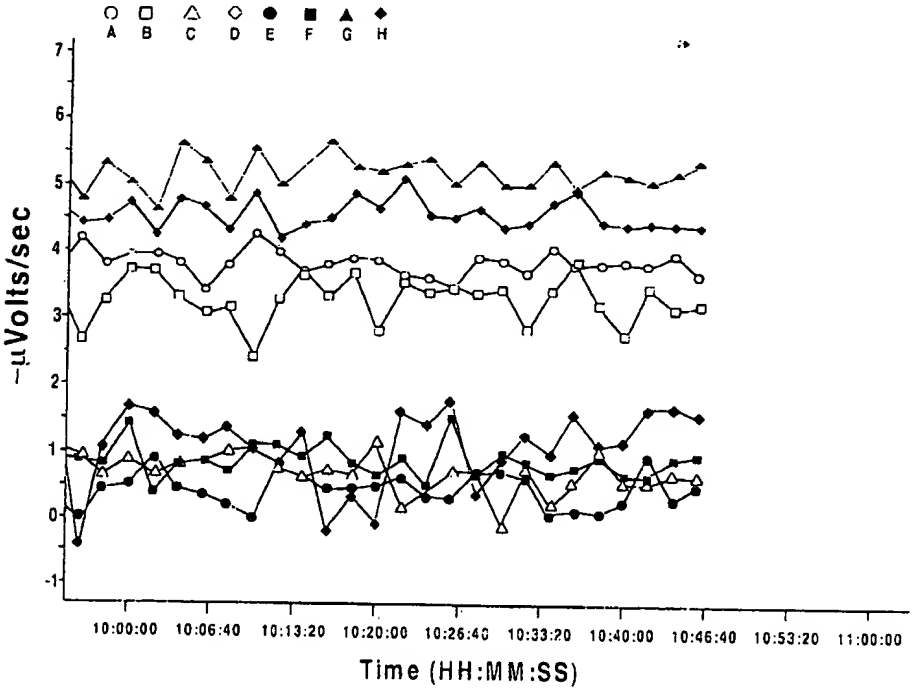

Fig. 6. Cytosensor microphysiometer (CMS) antileishmanial promastigote results after 17.5 h spiroconazole A treatment. The duplicate control parasite (i.e. parasites treated with drug solvent, 0.6% DMSO) tests, represented as uppermost lines, "G" and "H", have a consistently higher metabolic rate during the 11 h of observation. Parasites preincubated in parallel with controls for 17.5 h with 6.3- (lines "A" and "B"), 12.5- (lines "C" and "D"), and 50 µg ml^{-1} spiroconazole A (lines "E" and "F"), manifest lower metabolic rates, with the two highest drug concentrations resulting in metabolic rates very close to zero.

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Molluscicidal Pote

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RESULTS AND I

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compound (Table 1).
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A in DMSO was introduced into the wells in triplicate. Streptomycin at a concentration of 100 μg ml^{-1} was used as reference standard and 0.1 ml DMSO as a control. The plates were incubated at 37 °C and the diameter of zones of inhibition was measured across each well after 24 h. The MIC for bacteria was determined in trypticase soy broth to which were added serial 2-fold concentrations (0.025-200 μg ml^{-1}) of spiroconazole A. The tubes were inoculated in triplicate with 0.01-ml quantities of 6th broth cultures of the test isolates. The tubes were incubated at 37 °C for 24 h and examined spectrophotometrically at 530 nm. The lowest drug concentration that showed no turbidity was taken as the MIC. Streptomycin was used as the standard reference drug.

Molluscicidal Potency Test

Two local snail vectors; *Bulinus globosus* and *Biomphalaria pfeifferi*, were collected from a pond near Nkalagu Cement Factory in the Isielu Local Government Area of Enugu State, Nigeria and reared in our laboratory. Living snails were identified to species by the staff of the Department of Zoology, University of Nigeria. The residue from methanol extracts of *Dracaena* fruit pulp and spiroconazole A were separately dissolved in distilled water. This was made into a stock solution of 100 ppm before serial dilution to obtain desired concentrations. Molluscicidal tests were carried out according to Duncan and Sturrock (1987) using laboratory-reared snails. Tests were carried out in two replicates per test compound concentration. Ten snails (6-10 mm in height) were exposed for 24 h allowing 24 h for the recovery period after which mortality rate was determined. Tests to evaluate the effects of physicochemical factors (UV and pH) on the molluscicidal activity of spiroconazole A were carried out as described by Adewunmi and Marquis (1980).

RESULTS AND DISCUSSION

In a first activity-directed investigation, the methanol extracts of the fruit pulp of *D. mannii* and *D. arborea* exhibited strong antifungal and molluscicidal activities. Bioassay directed fractionation of this active fraction led to the isolation of a spiroconazole group of compounds. The antifungal activity of extracts of these plants was originally detected by direct spraying of TLC plates with a spore suspension of the test fungus *Cladosporium cucumerinum*. A clearly visible inhibition zone, even at the lowest concentration of 5 μg, was observed after using spiroconazole A (illustrated in Fig. 3). This concentration is below the detectable limit of the freqently used spray reagent (Godin, 1954) for saponins.

Spiroconazole A was tested for fungistatic, fungicidal and bacteriostatic activity against 17 species of fungi (results summarized in Table 1) and bacteria. These fungi, with the exception of *Cladosporium tennuisimum* and *Ramichloridium subulatum*, are well known either as strict or opportunistic pathogens of humans. The dermatophytes, causal agents of infections of hair, nail and skin, were inhibited at concentrations of 50 μg ml^{-1} or less, with Trichophyton soudanense manifesting greatest sensitivity to the drug (MIC; 6.25 μg ml^{-1}). The MICs for the species of pathogenic dermatiaceous fungi, causal agents of cutaneous and subcutaneous mycoses, were within the range 12.5-100 μg ml^{-1}. All the test yeasts species were inhibited at 100 μg ml^{-1} concentration or less, the most sensitive being Trichosporon cutaneum (MIC, 6.25 μg ml^{-1}). The minimum fungal concentrations were mostly 1-4 times the MIC values. The control antimycotics, ketoconazole and miconazole, commonly used in chemotherapy, showed lower MICs and MFCs relative to the test compound (Table 1). The result of the antibacterial test showed that spiroconazole A was selectively bacteriostatic against the gram-positive bacteria species at 10 X 10^3 μg ml^{-1} in

the agar assay method. In this study no antibacterial activity was observed at 200 μg ml^{-1} saponin in the MIC assay.

Spiroconazole A possesses strong molluscicidal activity against all the snail vectors. At 5 ppm concentration it exhibited 100% mortality within three h against four species of snails *Bulinus globosus, Bulinus forskalii, Biomphalaria pfeifferii,* and *Lymnaea natalensis,* while *Biomphalaria glabrata* were less susceptible to the 5 ppm lethal dose. However, spiroconazole A at 6 ppm yielded a 100% kill within 24 h against *Biomphalaria glabrata.* It is worthy of note that *Lymnaea natalensis,* which transmits the economically important major animal disease, fascioliasis, is killed within 3 h at 5 ppm lethal dose by spiroconazole A.

The results of the RAM test for leishmanial parasites are given in Fig. 4. After a 96-h incubation with spiroconazole A, no live parasites were observed in culture and RAM respiratory rates for all ^{14}C-substrates reflect this lack of parasite viability. The metabolic rate for every ^{14}C-substrate by the spiroconazole-treated parasites is near zero (solid black bars). The drug-treated results are in sharp contrast to the vehicle control (0.6% DMSO) treated promastigote ^{14}C-substrate catabolism, which show high respiratory rates during the 30-min test period (solid grey bars).

The results using the Cytosensor (Fig. 6) agree well with visual observation of the parasites by light microscopy given in Fig. 2, and the growth inhibition curve, Fig. 5. The vehicle control parasites, Fig. 2a, manifest the typical spindle-shaped monoflagellate form of leishmanial promastigotes. Cell density of the control parasites in culture was 5 X 10^7 ml^{-1}. Motility of the parasites was virtually 100%. Figure 2b shows parasites treated for 17.5 h at 6.3 μg ml^{-1} spiroconazole A. It is evident that at 6.3 μg ml^{-1} drug there are fewer parasites, about half that of the control culture, or 2.5 X 10^7 ml^{-1}, representing marked growth inhibition by spiroconazole A. At 12.5 μg ml^{-1} drug, Fig. 2c, the few remaining parasites are swollen, granulated, and the cytoplasm appears transparent, possibly indicating loss of membrane integrity with cytoplasmic leakage. Little to no motility was seen in parasites treated with 12.5 μg ml^{-1} spiroconazole A, and parasite number in culture was only 5 X 10^5 ml^{-1}. At 50 μg ml^{-1} drug, Fig. 2d, no intact parasites are visible, only hollow parasite membranes, with no cytoplasm. Likewise, an IC_{50} of approximately 10 μg ml^{-1} was observed for the growth inhibition data, Fig. 5. Maximum achievable serum level for SbV drugs, current "drugs-of-choice" for antileishmanial therapy, has been determined to be 20 μg ml^{-1} 1-2 h post-administration (references reviewed in Jackson, *et al.*, 1989, 1990).

Comparative analyses of the polar extracts from *Dracaena* species demonstrated that the spiroconazole analogues are the major biologically active components. These biological effects can perhaps explain the traditional use of the these plant species in treating different skin diseases.

The yield of biologically active saponins in *Dracaena* species is very high, estimated at up to 30% of the fruit pulp. The highest potency levels are localized in the fruit pulp and the molluscicidal material can be produced on a pilot scale. *Dracaenas* are propagated by seed or vegetatively by stem cutting and are drought resistant. Furthermore, the plant is abundant in west Africa (Keay *et al.*, 1964, Hutchinson and Dalziel, 1958) and is well known to the local population as a medicinal plant. The ease of cultivation of this plant will be a positive advantage over better known saponin-producing plants such as endod. The demand for steroid-based drugs such as cortisone and other corticosteroids, sex hormones, cardiotonic glycosides, oral contraceptives has steadily increased. Steroids of plant origin constitute a major part of the raw material for the preparation of such drugs. There is no doubt that the high yield of steroidal saponin from *Dracaena* spp. may serve as starting material for the manufacture of steroids of therapeutic interest.

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In conclusion, we have shown broad spectrum activity for spiroconazole A, having antibacterial, antifungal, antimalarial, antileishmanial, and molluscicidal properties. The drug concentration at which this compound acts compares very favorably with drug activity levels for current modern antibacterial, antifungal, antiparasitic, and molluscicidal drugs.

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INTRODUCTION

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BELL COMMUNICATIONS RESEARCH, INC., Plaintiff-Appellant,
v.
VITALINK COMMUNICATIONS CORPORATION, Defendant-Appellee.

No. 94-1516.

United States Court of Appeals, Federal Circuit.

May 23, 1995.

James S. Renard, Bickel & Brewer, Dallas, TX, argued for plaintiff-appellant. With him on the brief were William A. Brewer, III and Eric G. Calhoun.

Richard J. Anderson, Fish & Richardson, Minneapolis, MN, argued for defendant-appellee. With him on the brief was Wayne E. Willenberg.

Before MICHEL, RADER, and BRYSON, Circuit Judges.

MICHEL, Circuit Judge.

1 Bell Communications Research, Inc. ("Bellcore") appeals from the August 16, 1994 decision of the United States District Court for the District of New Jersey, No. 92-4104, granting summary judgment in favor of Vitalink Communications Corporation ("Vitalink") on the latter's counterclaim for a declaration of noninfringement and dismissing Bellcore's infringement suit against Vitalink. Because the trial court partially misconstrued the scope of the asserted claim of U.S. Patent No. 4,706,080 ('080), and consequently erred in granting summary judgment of noninfringement, we vacate and remand.

BACKGROUND

A. The Technology

2 Local Area Networks ("LANs") consist of a number of devices, such as computers or telephones, attached to a shared communications medium. The communications medium permits the devices to transmit bundles of data, or "packets," back and forth to one another. Such packets, which contain fields of information that function as source device and destination device addresses, are broadcast through the communications medium; only the device that recognizes its own address as the destination address receives the broadcast.

3 The quality of a LAN's performance degrades in proportion to both the number of devices in the network and the speed at which each device processes information. One can, however, recover some of this lost performance by creating networks of multiple LANs rather than simply adding devices to a single, larger LAN. These

« up multiple LANs are connected by means of "bridges," each of which are themselves composed of two paired "gateways." The gateways, each of which have memory capacity, maintain running lists of the source addresses of the packets they have forwarded, allowing the bridges they form gradually to "learn" how to broadcast packets selectively in order to reduce the network's overall load.

4 The existence of multiple pathways between a given pair of devices in two different LANs creates the potential for loops and thus thwarts the learning function of memory-capable gateways--a packet that cycles through a complete loop causes its source address to appear on both sides of the relevant gateway pairs, eliminating the advantage of equipping gateways to keep lists of source addresses from the packets they have broadcast. For purposes of describing and solving this looping problem, one can depict a group of interconnected networks as a graph, with lines and vertices used to represent connecting bridges and connected LANs, respectively. In this graphical notation, a "tree" is a graph in which a sequence of one or more lines connects two vertices, while a "spanning tree" is a graph in which all the vertices are connected. Such a spanning tree can be superimposed on the complete graph of the bridged networks and used to determine a set of loop-free spanning tree paths among the vertices. This process of determination can be accomplished either by some oversight mechanism or automatically by the bridges.

5 While the use of one spanning tree deals with multiple path and looping problems, two problems remain: spanning tree backup paths remain inactive unless bridge failures require that they be used, and the spanning tree's root may become a performance bottleneck for the system. The use of multiple spanning trees thus represents an improvement over the use of only one spanning tree. But one cannot implement a system for the use of multiple spanning trees without some means of differentiating among the spanning trees, such that a packet is always forwarded over some tree. A system can achieve the required differentiation in one of a number of ways: for example, the system could randomly assign different device addresses to different trees, or, alternatively, the source device could specify a tree by means of a tree identifier when it originates the packet.

B. The Patent in Suit

6 Bellcore's '080 patent, entitled "Interconnection of Broadcast Networks," discloses a method for interconnecting networks, such as LANs, that uses multiple concurrent spanning trees for packet delivery while preserving loop-free paths. According to the summary of the invention contained in the specification,

7 [e]ach spanning tree is uniquely identified. Each message packet that traverses the overall system is assigned to a specific spanning tree so the packet travels between nodes [i.e., device networks] along edges [i.e., bridges] contained in the specified spanning tree. Each gateway, with an expanded store-and-forward protocol [in its memory], parses the packet to determine the assigned spanning tree and forwards the message accordingly. In one embodiment of the present invention, the device originating the packet specifies the spanning tree identifier and conveys it either explicitly or implicitly in the packet.

8 Col. 2, 11. 14-25. As the more detailed description explains,

9 To implement the improvement in the gateway protocol arrangement in accordance with one aspect of the present invention, a set of spanning trees is

« up elected for the cyclic graph according to predetermined guidelines. Each spanning tree is assigned a unique identifier or number and each message traversing the system is assigned to a unique spanning tree via its identifier. Any gateway receiving this message determines the tree number and then routes the message over the specified spanning tree and drops all packets of other spanning trees. Typically, the device originating the message specifies the spanning tree number, either explicitly or implicitly. For instance, with the explicit approach, a "tree number" field could be added to the packet specifications, say as an extra bit in the header of the packet. With the implicit approach, a spanning tree number could be generated from fields normally occurring in the packet such as the source and destination addresses. An appropriate example function might be

10 spanning tree number = (source 'exclusive or' destination) modulo N,

11 where N is the number of spanning trees in the network. This has the benefit that all traffic between a pair of hosts will travel on only one spanning tree, thus minimizing the occupied drop lists across the system.

12 Col. 5, ll. 11-35. Bellcore's method also preserves the "transparency" of the interconnections among the LANs, according to which the existence of gateways does not require modifications to the networked devices or the packets they broadcast. Col. 1, ll. 29-35.

13 Claim 6 of the '080 patent, the only claim asserted by Bellcore, reads as follows:

14 6. A method for transmitting a packet over a system comprising a plurality of networks interconnected by gateways, said packet originated by a source device connected to one of said networks and destined for a destination device connected to one of said networks, said packet including a source address and a destination address, and said method comprising the steps of

15 defining an undirected graph representative of the system wherein said networks comprise graph nodes and said gateway[s] comprise graph paths,

16 defining a spanning tree on said graph such that every pair of said nodes is connected by only one of said paths and selecting a plurality of spanning trees for said graph according to pre-determined system guidelines,

17 configuring each gateway with source address lists in correspondence to the number of trees having said each gateway comprising one of said paths, wherein said lists reduce to a common list whenever said selection of spanning trees results in identical ones of said lists for said each gateway,

18 assigning, by said source device, one of said trees to broadcast said packet and associating with said packet an identifier indicative of said one of said trees,

19 broadcasting said packet by said source device through the system on said one of said trees, and

20 for each gateway receiving said packet,

21 (i) determining for each said packet said source address, said destination address and said packet identifier,

22 (ii) if said receiving gateway does not process packets having said identifier,

« up inhibiting forwarding of said packet; otherwise, inserting said source address in the corresponding one of said lists associated with said identifier, and

23 (iii) inhibiting forwarding of said packet if said destination address is in said corresponding list; otherwise, forwarding said packet by said receiving gateway.

24 Col. 10, ll. 18-57.

C. The Accused Products

25 Vitalink manufactures and markets communications products, including bridges and bridge-routers used in the networking of LANs. Specifically, Vitalink sells a series of products including a Distributed Load Sharing ("DLS") feature, which is itself the subject of a Vitalink patent. These products are alleged by Bellcore to use the method claimed in the '080 patent.

26 Both Bellcore and Vitalink agree that, in a Vitalink product using the DLS feature, a message packet contains both a source address and a destination address but no separate packet identifier. In other words, DLS uses only the implicit approach to spanning tree identification in the packet. The parties also agree that the tree along which a message packet travels in a DLS system may change mid-course in response to such phenomena as link failures and the opening of additional links or, when the system is in a steady state, remain the same throughout its transmission from the source device to the destination device.

D. The Infringement Suit

27 Bellcore originally sued Vitalink in the Eastern District of Virginia, alleging, among other things, that Vitalink's DLS products infringe Claim 6 of the '080 patent, either literally or under the doctrine of equivalents. Vitalink counterclaimed for a declaration of, among other things, noninfringement. After the case was transferred from Virginia to New Jersey on Vitalink's motion, the parties exchanged extensive written discovery, including affidavits from opposing computer science experts. After the close of discovery, Vitalink moved for summary judgment on its counterclaim for a declaration of noninfringement, contending that "in the DLS system a message packet is not assigned to a specific spanning tree by a source device as required by claim 6 ... [and] a spanning tree identifier is not associated with the message packet as required by claim 6."The district court, in a letter opinion dated August 16, 1994, granted Vitalink's motion for summary judgment of noninfringement and dismissed Bellcore's complaint. The court's decision in Vitalink's favor followed from its construction of Claim 6, according to which "the language of Claim 6 reveals that the Claim 6 packet literally requires three separate elements: (1) a source address, (2) a destination address, and (3) a packet identifier." Slip op. at 9. In addition, the district court construed Claim 6 to require that the source device assign, prior to transmission, the one spanning tree along which the packet travels to its specified destination. Id. at 8. Having construed Claim 6 to require both the assignment of one and only one spanning tree route prior to broadcast and the insertion into the packet of a spanning tree identifier separate from the destination and source addresses, the district court concluded that Bellcore could not make out a case of literal infringement against Vitalink. According to the district court, "the accused Vitalink DLS products, while having a source address and a destination address, do not employ a packet identifier contained within its packet such that the all elements or all limitations rule of literal

« up ıfringement cannot be satisfied in the present case." Id. at 10-11. Similarly, with ..espect to the assignment step of Claim 6, the court noted that "Bellcore has effectively conceded that after the message packet has been broadcast by [a Vitalink] DLS source device, events might well intervene to alter the packet's route in mid-course ... and hence the source device has no ability to assign[ ] the spanning tree along which the message packet is to be routed," id. at 11-12, again precluding literal infringement. Finally, the district court concluded that Bellcore's claim of infringement under the doctrine of equivalents was legally deficient.

28 Bellcore appeals from the district court's decision, contending that Claim 6, when properly construed, covers both the explicit and implicit approaches to spanning tree identification in the packet, as described in the specification, and neither provides for nor rules out the possibility of mid-course alterations in a packet's path within a system embodying the claimed method.

DISCUSSION

29 The moving party is entitled to summary judgment under Federal Rule of Civil Procedure 56(c) "if the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, show that there is no genuine issue as to any material fact and that the moving party is entitled to a judgment as a matter of law." FED.R.CIV.P. 56(c). We review the district court's grant of summary judgment de novo, Conroy v. Reebok Int'l, Ltd., 14 F.3d 1570, 1575, 29 USPQ2d 1373, 1377 (Fed.Cir.1994), resolving all doubt respecting the presence or absence of genuine factual issues in the nonmovant's favor, Union Carbide Corp. v. American Can Co., 724 F.2d 1567, 1571, 220 USPQ 584, 588 (Fed.Cir.1984). Finally, the disposition of this appeal turns largely on whether the trial court properly construed Claim 6 of the '080 patent, a question of law that we review de novo. Markman v. Westview Instruments, Inc., 52 F.3d 967, 978-80, 34 USPQ2d 1321, 1329 (Fed.Cir.1995) (in banc).

A. Claim Construction

30 Before turning to the parties' contentions about the proper construction of the asserted claim, it is important to review some basic principles of claim construction. First, and most importantly, the language of the claim defines the scope of the protected invention. Yale Lock Mfg. Co. v. Greenleaf, 117 U.S. 554, 559, 6 S.Ct. 846, 847, 29 L.Ed. 952 (1886) ("The scope of letters-patent must be limited to the invention covered by the claim, and while the claim may be illustrated it cannot be enlarged by language used in other parts of the specification."); Autogiro Co. of Am. v. United States, 384 F.2d 391, 396, 155 USPQ 697, 701 (Ct.Cl.1967) ("Courts can neither broaden nor narrow the claims to give the patentee something different than what he set forth [in the claim]."). See also Continental Paper Bag Co. v. Eastern Paper Bag Co., 210 U.S. 405, 419, 28 S.Ct. 748, 751, 52 L.Ed. 1122 (1908); Cimiotti Unhairing Co. v. American Fur Ref. Co., 198 U.S. 399, 410, 25 S.Ct. 697, 702, 49 L.Ed. 1100 (1905). Accordingly, "resort must be had in the first instance to the words of the claim," words to which we ascribe their ordinary meaning unless it appears the inventor used them otherwise. Envirotech Corp. v. Al George, Inc., 730 F.2d 753, 759, 221 USPQ 473, 477 (Fed.Cir.1984). Second, it is equally "fundamental that claims are to be construed in the light of the specifications and both are to be read with a view to ascertaining the invention." United States v. Adams, 383 U.S. 39, 49, 86 S.Ct. 708, 713, 15 L.Ed.2d 572 (1966). See also Markman, 52 F.3d at 978-80, 34

« up [SPQ2d at 1329-30 ("Claims must be read in view of the specification, of which they are a part.... For claim construction purposes, the [specification's] description may act as a sort of dictionary, which explains the invention and may define terms used in the claims.").

31 We construe claim preambles, like all other claim language, consistently with these principles. Much ink has, of course, been consumed in debates regarding when and to what extent claim preambles limit the scope of the claims in which they appear. See, e.g., 2 DONALD S. CHISUM, PATENTS Sec. 8.06[d] (1993); 1 ANTHONY W. DELLER, PATENT CLAIMS Secs. 78, 163-83 (2d ed. 1971); Willis Higgins, The Significance of Preambles in Chemical Composition Claims, 49 J.PAT. & TRADEMARK OFF. SOC'Y 337 (1967); Vincent Millin, PTO Practice: Preamble--Prelude to Patentability, 72 J.PAT. & TRADEMARK OFF. SOC'Y 348 (1990); David R. Pressman, Note, Patents--Claim Construction, 30 GEO.WASH.L.REV. 380 (1961); Alton D. Rollins, Is It New or Not?, 68 J.PAT. & TRADEMARK OFF. SOC'Y 89 (1986). These debates center, however, on particular arts and claiming styles and do not call into doubt the general principle, as well-settled as any in our patent law precedent, that a claim preamble has the import that the claim as a whole suggests for it. In other words, when the claim drafter chooses to use both the preamble and the body to define the subject matter of the claimed invention, the invention so defined, and not some other, is the one the patent protects. In re Paulsen, 30 F.3d 1475, 1479, 31 USPQ2d 1671, 1673 (Fed.Cir.1994) ("[T]erms appearing in a preamble may be deemed limitations of a claim when they give meaning to the claim and properly define the invention.") (internal quotation omitted); London v. Carson Pirie Scott & Co., 946 F.2d 1534, 1539, 20 USPQ2d 1456, 1459 (Fed.Cir.1991) ("The shank is defined in the preamble as that portion of the hanger 'between the supporting hook for the hanger and the support for the garment.' This is not merely a suggested use or 'clarifying language,' as London argues, but rather a limitation supported by structure which must be satisfied by Samsonite's clamp, either literally or equivalently[,] if infringement is to be found."); In re Stencel, 828 F.2d 751, 754, 4 USPQ2d 1071, 1073 (Fed.Cir.1987) ("Whether a preamble of intended purpose constitutes a limitation to the claim is, as has long been established, a matter to be determined on the facts of each case in view of the claimed invention as a whole."); Loctite Corp. v. Ultraseal Ltd., 781 F.2d 861, 866, 228 USPQ 90, 92 (Fed.Cir.1985) ("Although it appears in the preambles of the '012 patent claims, the term 'anaerobic' breathes life and meaning into the claims and, hence, is a necessary limitation to them."); Perkin-Elmer Corp. v. Computervision Corp., 732 F.2d 888, 896, 221 USPQ 669, 675 (Fed.Cir.) ("The system of claim 1 is one of unity magnification and is image forming. Those limitations appear in the preamble, but are necessary to give meaning to the claim and properly define the invention."), cert. denied, 469 U.S. 857, 105 S.Ct. 187, 83 L.Ed.2d 120 (1984). One of our predecessor courts summarized this approach in Kropa v. Robie, 187 F.2d 150, 88 USPQ 478 (CCPA 1951), after reviewing some 37 cases that turned on the limiting nature of the preambles to the claims in suit. According to the court in Kropa,

32 the preamble has been denied the effect of a limitation where ... the claim or [interference] count apart from the introductory clause completely defined the subject matter [of the invention], and the preamble merely stated a purpose or intended use of that subject matter. On the other hand, in those ... cases where the preamble to the claim or count was expressly or by necessary implication given the effect of a limitation, the introductory phrase was deemed essential to point out the invention defined by the claim or count. In the latter class of cases, the preamble

« up 'as considered necessary to give life, meaning and vitality[1] to the claims or counts.

33 Id. at 152, 88 USPQ at 480-81. Preamble construction thus presents no deeper mystery than the broader task of claim construction, of which it is but a part.

B. Claim 6 of the '080 Patent

34 Claim 6 of the '080 patent recites a "method for transmitting a packet over a system comprising a plurality of networks ... said packet including a source address and destination address," as its preamble indicates. It then recites, inter alia, the steps of "assigning, by said source device, one of said trees to broadcast said packet and associating with said packet an identifier indicative of said one of said trees." (Emphasis added). These two steps of the claimed method, by referring to "said packet," expressly incorporate by reference the preamble phrase "said packet including a source address and a destination address." As a result, only a method for transmitting packets that have both source and destination addresses can literally infringe Claim 6.

35 Bellcore contends, as it did before the district court, that one ought not to accord "definitional status" to the phrase "said packet including a source address and a destination address" because it appears in the claim's preamble, relying primarily on our decision in DeGeorge v. Bernier, 768 F.2d 1318, 226 USPQ 758 (Fed.Cir.1985), for the proposition that "[t]he preamble to a claim does not limit the claim." Bellcore likely maintains this position on the mistaken belief that to do otherwise would be to concede its case against Vitalink. In any event, however, Bellcore's position is untenable. In DeGeorge, we noted that "[g]enerally, and in this case, the preamble does not limit the claims." Id. at 1322 n. 3, 226 USPQ at 761 n. 3. As the preceding discussion of our cases on claim preambles makes clear, this observation in DeGeorge can only have been de scriptive, rather than pre scriptive. We have long eschewed the use of an absolute rule according or denying all preambles limiting effect, having recognized that one cannot determine a preamble's effect except by reference to the specific claim of which it is a component. Claim 6, as drafted and in light of the specification, is plainly limited such that it literally reads only on methods that transmit packets having both source and destination addresses.[2]

36 The district court further concluded that the above limitation regarding the contents of the packet compels one to construe the step of "associating with said packet an identifier" to require that the identifier be separate and distinct from the destination address; Vitalink urges us to affirm this construction of the claim. In other words, Vitalink would have us read the phrase "associating with said packet an identifier" as if it were "inserting into said packet a separate identifier." This construction of the claim is, however, no more tenable than Bellcore's. For, while nothing within Claim 6 considered in isolation impeaches the construction that Vitalink prefers, it is legal error to construe a claim by considering it in isolation. A claim must be read in view of the specification of which it is a part. Adams, 383 U.S. at 49, 86 S.Ct. at 713; Markman, 52 F.3d at 978-80, 34 USPQ2d at 1329-30. The specification of the '080 patent makes it clear to one of ordinary skill in the art that one can "associat[e]" an identifier with a packet within the meaning of Claim 6 either explicitly (e.g., by the insertion of an additional "tree number" field into the packet) or implicitly (e.g., by the insertion of a destination address field from which a tree number can be determined). Thus, the associating step of Claim 6 covers both an implicit or an explicit approach. The district court, by construing it to cover the

« up xplicit approach alone, read an additional limitation into the claim, an error of law. ~ee, e.g., Specialty Composites v. Cabot Corp., 845 F.2d 981, 988, 6 USPQ2d 1601, 1606 (Fed.Cir.1988).

37 Bellcore also contends that the district court erred when it interpreted the assigning step of Claim 6 to require that the source device assign the packet to be broadcast along one and only one spanning tree, on which the packet would travel to its destination without any mid-course changes in tree assignment. We, however, share the trial court's view of the assigning step's proper construction. The claim first recites the step of "assigning, by said source device, one of said trees to broadcast said packet." Although this clause appears to include no limitation regarding the possibility that mid-course changes in tree assignment might occur, the remainder of the claim renders such a construction of Claim 6 unworkable. First, the broadcasting step, according to which the packet is sent "through the system on said one of said trees," strongly suggests that the packet travels on the same tree, assigned at the outset, from its source to its destination. Second, and more importantly, the claimed method whereby the gateways execute their store-and-forward protocol precludes mid-course changes in tree assignment. According to the claim, each gateway receiving the packet "determin[es] for each said packet ... said packet identifier"--that is, the identifier associated with the packet that is "indicative of said one of said trees" on which the packet has been broadcast. Each gateway then executes its first inhibit-or-forward decision according to whether it "process[es] packets having said identifier"--again, the identifier associated with the packet that is "indicative of said one of said trees" on which the packet has been broadcast. Thus, the identifier that indicates the "one of said trees" along which the packet is broadcast "through the system" remains the same throughout the packet's trip from its source to its destination. As a consequence, in the claimed method, the tree on which the packet travels must also remain the same: if the packet were assigned to a new tree mid-course, the gateways along that new tree would not forward it, inasmuch as they do not process packets having the identifier, indicative of a different tree, that was associated with the packet prior to its broadcast. The district court properly construed Claim 6 to require that the source device assign, prior to transmission, the one spanning tree along which the packet travels to its specified destination.

C. Summary Judgment of Noninfringement

38 The district court's decision to grant Vitalink's summary judgment motion flowed from its construction of the scope of Claim 6. Specifically, as we noted above, having construed the associating step of Claim 6 to require the insertion into the packet of a spanning tree identifier separate from the destination and source addresses, the court concluded that Bellcore could not make out an infringement case, literal or by equivalents, against Vitalink. Because that construction was erroneous, the court's reliance on the associating step as a basis for its summary judgment ruling was necessarily in error.

39 The district court also concluded that since the claimed method assigns the one spanning tree along which the packet travels to its specified destination and Vitalink's DLS system allows for mid-course corrections, Bellcore's literal infringement claim was legally defective as to the assigning step of Claim 6. Although the court's construction of the assigning step was correct, it does not necessarily follow that Bellcore's infringement claim against Vitalink must fail, because the

« up ecord does not make it clear that Vitalink's DLS system never uses the claimed method. While we express no view on the ultimate question whether Vitalink's DLS system infringes Claim 6, either literally or by equivalents, it should be noted that any future infringement analysis respecting the assigning step should be undertaken with due attention to the principle that an accused product that sometimes, but not always, embodies a claimed method nonetheless infringes. See Paper Converting Mach. Co. v. Magna-Graphics Corp., 745 F.2d 11, 20, 223 USPQ 591, 597 (Fed.Cir.1984) ("[I]mperfect practice of an invention does not avoid infringement."); Roche Prods., Inc. v. Bolar Pharmaceutical Co., 733 F.2d 858, 861, 221 USPQ 937, 939 (Fed.Cir.) ("Section 271(a) [of Title 35] prohibits, on its face, any and all uses of a patented invention."), cert. denied, 469 U.S. 856, 105 S.Ct. 183, 83 L.Ed.2d 117 (1984).

40 The court's error in claim construction vitiates its conclusions as to Bellcore's ability to succeed on its infringement claims on the present limited summary judgment record. The declaratory judgment of noninfringement in favor of Vitalink must therefore be vacated.

CONCLUSION

41 Accordingly, we vacate the district court's summary judgment in Vitalink's favor and remand the case for proceedings on the issue of infringement, literal or by equivalents, consistent with this opinion.

VACATED AND REMANDED

COSTS

42 Each party to bear its own costs.

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[1] This particular phrase originates in Schram Glass Manufacturing Co. v. Homer Brooke Glass Co., wherein the court observed that a claim preamble "may entirely fail to supply a necessary element in a combination, yet it may so affect the enumerated elements as to give life and meaning and vitality to them, as they appear in the combination." 249 F. 228, 232-33 (7th Cir.), cert. denied, 247 U.S. 520, 38 S.Ct. 582, 62 L.Ed. 1246 (1918)

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[2] The claim cannot literally read on a method for transmitting packets that, for example, lack source addresses

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78 F.3d 1575

38 U.S.P.Q.2d 1126

HOECHST CELANESE CORPORATION, Plaintiff-Appellee,
v.
BP CHEMICALS LIMITED and Sterling Chemicals, Inc.,
Defendants-Appellants.

No. 94-1472.

**United States Court of Appeals,
Federal Circuit.**

March 19, 1996.

Appealed from U.S. District Court for the Southern District of Texas (Galveston), Samuel B. Kent, Judge.

John F. Lynch, Arnold, White & Durkee, Houston, Texas, argued for plaintiff-appellee. With him on the brief were Michael Macklin, Melinda L. Patterson, Richard L. Stanley and Russell L. Sandidge. Also on the brief were Kenneth A. Genoni, Hoechst Celanese Corporation, Somerville, New Jersey, and Michael W. Ferrell, Hoechst Celanese Corporation, Summit, New Jersey. Of counsel were Stephen D. Dellett and Stephen E. Edwards.

Clyde F. Willian, Willian Brinks Hofer Gilson & Lione, Chicago, Illinois, argued for defendants-appellants. With him on the brief were Jack C. Beringweig, Cynthia A. Homan, Richard A. Kaplan and Dominic P. Zanfardino. Also on the brief were Harold Haidt and G.T. Delahunty, Brooks Haidt Haffner & Delahunty, New York City, and Robins C. Gibbs and John Christopher Reynolds, Gibbs & Bruns, L.L.P., Houston, Texas.

Before PAULINE NEWMAN, CLEVENGER, and RADER, Circuit Judges.

PAULINE NEWMAN, Circuit Judge.

1 BP Chemicals Limited and Sterling Chemicals, Inc. (together "BP") appeal the judgment of the United States District Court for the Southern District of Texas,[1] entered on the jury verdict that BP had infringed, willfully, United States Patent No. 4,615,806 (the '806 patent) owned by Hoechst Celanese Corporation (herein "Celanese"). On re-determination of the issues of claim interpretation, as mandated by Markman v. Westview Instruments, Inc., 52 F.3d 967, 34 USPQ2d 1321 (Fed.Cir.) (en banc), cert. granted, --- U.S. ----, 116 S.Ct. 40, 132 L.Ed.2d 921 (1995), and on review of the other issues on appeal, the judgment is affirmed.

2 * INFRINGEMENT

A. The Invention

3 The '806 patent, inventor Dr. Charles B. Hilton, is directed to a method of reducing iodide contamination in organic medium, particularly acetic acid. When the acetic acid is catalytically converted to vinyl acetate, the presence of iodide in more than about one part per billion poisons the catalyst. Such iodide contamination was known to be removable by contacting the acetic acid with silver-charged gel ion

« up xchange resins, but the process was slow and impractical in large commercial . olume. In seeking to improve the Celanese commercial process, Dr. Hilton discovered that by using a macroreticulated (sometimes described as macroporous) silver-charged cation exchange resin having specified characteristics, he obtained effective, rapid, large-volume removal of minute traces of iodine, to a degree of effectiveness, practicality, and utility not previously available.

4 When BP encountered iodide contamination in the commercial production of acetic acid BP sought other methods of removal before adopting the method, using a macroreticulated silver-charged cation exchange resin, that is charged with infringement. Celanese brought suit, asserting that the BP method infringed claims 2 and 6 of the '806 patent. Claim 2 is shown, with claim 1 from which it depends:

5 1. A method for removing iodide compounds from a non-aqueous organic medium comprising contacting the medium containing said iodide compounds with an ion exchange resin characterized in that the resin is a macroreticulated strong-acid cation exchange resin which is stable in the organic medium and has at least one percent of its active sites converted to the silver or mercury form.

6 2. The method of claim 1 wherein the non-aqueous organic medium is acetic acid and from about 25 to about 75 percent of the active sites are in the silver form.

7 The question of infringement turns on the meaning of the word "stable" in the claims. It is no longer disputed that all of the other claim elements and limitations are present in the BP method.

B. Review Procedure

8 Trial was to a jury, lasting for seven days. The jury found that the '806 patent was infringed and that the infringement was willful. The district court, denying duly made motions for a new trial and for judgment as a matter of law, entered judgment on the jury verdict. In its opinion the court identified the evidence in support of the jury verdict, identified the evidence supporting each party's theory of the meaning of certain disputed terms in the patent, and stated its own view of the meaning of these terms. In following this procedure the court relied on Read Corp. v. Portec, Inc., 970 F.2d 816, 822 n. 3, 23 USPQ2d 1426, 1432 n. 3 (Fed.Cir.1992), as requiring or advising that a judicial statement be made of the meaning of disputed claim terms.

9 BP points out that Read v. Portec has been superseded by the decision in Markman v. Westview Instruments, Inc., 52 F.3d 967, 34 USPQ2d 1321 (Fed.Cir.) (en banc), cert. granted, --- U.S. ----, 116 S.Ct. 40, 132 L.Ed.2d 921 (1995), and that Markman requires the Federal Circuit to decide de novo disputed questions of claim interpretation without deference to the trier of fact. BP points out that the disputed question of the meaning of the claim term "stable" is dispositive of the issue of infringement, and therefore that no deference need be given to the jury's finding of infringement. We agree that Markman so requires, and that the issue of infringement is decided by the meaning of "stable" as used in the claims. See Markman, 52 F.3d at 999, 34 USPQ2d at 1346 (Pauline Newman, J., dissenting) (pointing out that the disputed meaning of technical terms often decides the fact of infringement).

10 "Stable" is defined in the body of the specification as turning on the meaning of "dimension." Although "dimension" appears in the specification, not in the claims,

« up nplementation of the Markman decision appears to require that the meaning of dimension" be given the same de novo determination by the Federal Circuit as the meaning of "stable" in the claims, lest we add further complexities to the trial of patent cases.

11 C. Construction of the Terms "Stable" and "Dimension"

12 A technical term used in a patent document is interpreted as having the meaning that it would be given by persons experienced in the field of the invention, unless it is apparent from the patent and the prosecution history that the inventor used the term with a different meaning. ZMI Corp. v. Cardiac Resuscitator Corp., 844 F.2d 1576, 1579, 6 USPQ2d 1557, 1560 (Fed.Cir.1988); Intellicall, Inc. v. Phonometrics, Inc., 952 F.2d 1384, 1387, 21 USPQ2d 1383, 1386 (Fed.Cir.1992).

13 The meaning of "stable" as used in the claims is defined in the specification, col. 4, lines 31-35, as follows:

14 By the term "stable," it is meant that the resin will not chemically decompose, or change more than about 50 percent of its dry physical dimension upon being exposed to the organic medium containing the iodide compounds.

15 Thus the meaning of "stable" depends on the meaning of "dry physical dimension." On the BP position that "dry physical dimension" refers to volume, the BP process does not infringe; but on the Celanese position that "dimension" is a linear measure, there is literal infringement. Celanese states that linear dimension is the plain meaning of "dimension" as understood by persons of skill in this field and as used by the inventor. The BP position is that the term "stable" refers to volume as the physical dimension being measured, pointing out that the resin is in the shape of spherical beads and that the inventor in his research measured volume change. BP states that since its resin changes by more than 50% in volume when exposed to acetic acid, there can not be infringement.

16 The parties have provided us with photographs and experimental data, the testimony of the scientists who produced the data and interpreted it, and the testimony of experts in the field. Markman limits appellate reliance on extrinsic evidence to evidence in explanation of the technology and technical terms:

17 Through this process of construing claims by, among other things, using certain extrinsic evidence that the court finds helpful and rejecting other evidence as unhelpful, and resolving disputes en route to pronouncing the meaning of claim language as a matter of law based on the patent documents themselves, the court is not crediting certain evidence over other evidence or making factual evidentiary findings. Rather, the court is looking to the extrinsic evidence to assist in its construction of the written document, a task it is required to perform.

18 52 F.3d at 981, 34 USPQ2d at 1331. However, we have found it necessary to rely on the evidence presented at the trial and credit certain evidence over other evidence, for we are not personally qualified to know the scientific meanings of "stable" and "dimension" as applied to macroreticulated cation-exchange resins in organic medium.

19 The evidence was sharply in conflict. The technical expert presented by Celanese testified as follows:

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Q. The second part of this has to do with its dimension. What does that mean?

21 A. For the case of a spherical resin, it typically means its diameter.

22 Q. The word "dimension," does it mean volume dimension?

23 A. There is no such thing as volume dimension.

24 In turn, the BP expert testified that "dimension" meant volume dimension, stating that volume is what one skilled in the art would understand the term to mean:

25 Q. Okay. Is that all the reasons [why you believe the term "stable" refers to volume]?

26 A. There are at least two, perhaps three, additional very important reasons. One is that really it is the common practice of measuring changes that a resin experiences as it swells in a solvent in terms of volume percentage swelling. That is very amply documented in the literature. It is the easiest thing to do. Conversely, it is rather difficult to pick a single bead, measure the change in diameter of that bead, for example, because not every one bead in a sample of resin is identical to the rest of the beads....

27 ....

28 * * *

29 The other rather important reason is that it is clearly the objective of this patent to distinguish between a resin that works because it has a porosity independent of swelling, such as Amberlyst 15, and another type of resin which has a porosity that depends upon swelling. That would be the gel type resin in the language used by the patent.

30 Both sides cite dictionary definitions that support their respective positions. Webster's Ninth New Collegiate Dictionary at 355 (1988) defines "dimension" as:

31 measure in one direction; specif. one of three coordinates determining a position in space or four coordinates determining a position in space and time.

32 In partial contrast, the Concise Oxford Dictionary of Current English at 327 (8th ed.1990) defines "dimension" as:

33 a measurable extent of any kind, as length, breadth, depth, area, and volume.

34 This court has occasionally relied on general and technical dictionaries to determine the meaning of technical and other terms. In this case the dictionaries do not distinguish in a dispositive manner between the contested technical meanings. Further, a general dictionary definition is secondary to the specific meaning of a technical term as it is used and understood in a particular technical field. See Hormone Research Found., Inc. v. Genentech, Inc., 904 F.2d 1558, 1563, 15 USPQ2d 1039, 1043-44 (Fed.Cir.1990), cert. dismissed, 499 U.S. 955, 111 S.Ct. 1434, 113 L.Ed.2d 485 (1991). Thus we return to the testimony at trial.

35 Dr. Hilton, the inventor, testified under direct examination as follows:

36 Q. What is meant by that sentence? In other words, how much swelling does that definition of stable accommodate?

« up A. A 50 percent change in dimension. The dimension is a distance. A dimension is ..ot volume. Okay? It's the distance between my hands, or it's the distance across my chest. It's the radius of a sphere. A dimensional change in a spherical particle of 50 percent would lead to a swelling or a volume increase of 337 percent.

38 Dr. Hilton was challenged as to his assertion that "dimension" means distance or linear dimension, for he had measured the swelling volume of these resins during his research. The following exchange occurred on cross-examination:

39 Q. When did you first form a view that dimension means something other than volume dimension, dimension in this definition of stable?

40 A. I have never thought of volume as being a dimension. Dimension is not--volume is not a dimension. Volume of a sphere formula, four thirds pi, distance cubed, radius cubed, distance times distance times distance. Dimension is a distance.

41 Q. You've never heard the term "volume" used as a dimension?

42 A. No.

43 Q. Yet you consider the volume expansion in order to design a guard bed, do you not?

44 A. Yes, you do.

45 Q. How many dimensions does volume have?

46 A. Volume has three dimensions.

47 The district court called Dr. Hilton's testimony "highly credible." Although we are at a disadvantage in attempting to make credibility determinations, the inventor's testimony reads as that of an expert in the field. See Palumbo v. Don-Joy Co., 762 F.2d 969, 976, 226 USPQ 5, 9 (Fed.Cir.1985) (concluding that particular inventor's declaration as to claim meaning was by a "knowledgeable declarant"), overruled on other grounds, Markman, 52 F.3d at 979, 34 USPQ2d at 1329. Markman requires us to give no deference to the testimony of the inventor about the meaning of the claims. Id. at 983, 52 F.3d 967, 34 USPQ2d at 1332. However, we have treated Dr. Hilton's testimony as cumulative to the other evidence, and as enlarging our understanding of the technology and the usage of the disputed terms.

48 In addition, the specification of the '806 patent shows the resin characteristic of mesh size of the dry resin, a linear measure based on diameter. The specification also contains swelling data stated to be from the Technical Bulletin for Amberlyst TM 15 and which, according to the inventor's testimony, is the percentage of swelling by volume. A videotaped "swelling test" that was presented to the jury is stated to have shown that Celanese's preferred Amberlyst TM 15 resin expanded slightly more than 50% by volume in acetic acid, while BP's Purolite TM resin of the same chemical composition (polystyrene cross-linked with divinylbenzene) expanded 103% by volume but less than 50% in linear dimension upon exposure to acetic acid.

49 The district court observed that BP's interpretation of "stable" as meaning dimension by volume would exclude from the claims the Celanese preferred

« up mbodiment that is described in the specification. However, if stable is measured by ..near dimension, the claims include the resin that Celanese specifies in its invention. We share the district court's view that it is unlikely that an inventor would define the invention in a way that excluded the preferred embodiment, or that persons of skill in this field would read the specification in such a way. See Modine Mfg. Co. v. United States Int'l Trade Comm'n, 75 F.3d 1545, 1550, 37 USPQ2d 1609, 1612 (Fed.Cir.1996) (claim interpretation that would exclude the inventor's device is rarely the correct interpretation).

50 We find that the more reasonable explanation is that volume has three dimensions, and we give weight to the argument that on the BP definition the Celanese preferred embodiment would not be within the claims of the Celanese patent. Thus we conclude that "dry physical dimension" as used in the specification means linear dimension. On this definition of dimension, and defining "stable" accordingly, the claims read literally on the BP process.

D. The Issues of Equivalency

51 Since this case was tried before Markman was decided, the jury was instructed to interpret these disputed terms en route to its verdict on the issue of infringement. We thus turn to the jury trial, in the interest of complete review at this time.

52 BP argues that a new trial is required because the jury was not asked to distinguish between literal infringement and infringement by equivalency. BP states that because it is possible that the jury relied on an inapplicable theory of infringement, the verdict must be discarded.

53 Celanese had proposed the submission to the jury of separate questions on literal infringement and infringement by equivalency, while BP did not propose separate questions. The judge selected the BP form of verdict. The specificity of the verdict is within the discretion of the trial judge. Allen Organ Co. v. Kimball Int'l, Inc., 839 F.2d 1556, 1561, 5 USPQ2d 1769, 1773 (Fed.Cir.) ("District courts have broad discretion in the conduct of jury trials, including the form of the jury verdict."), cert. denied, 488 U.S. 850, 109 S.Ct. 132, 102 L.Ed.2d 104 (1988). BP concedes that it had proposed the form of the verdict that was used, and states that the reason it did not propose a separate question on equivalency was because of its position that equivalency was an equitable matter and not for the jury. However, BP was fully apprised that the jury was instructed on infringement by equivalency, and that the issue had been presented by witnesses at trial. Further, BP's position was not the law at the time of trial, nor is it now. Hilton Davis Chem. Co. v. Warner-Jenkinson Co., 62 F.3d 1512, 35 USPQ2d 1641 (Fed.Cir.1995) (en banc).

54 BP by its acquiescence in and indeed by its proposal of the verdict form waived objection to the verdict form. See Fed.R.Civ.P. 51; Allen Organ, 839 F.2d at 1562, 5 USPQ2d at 1774 (applying the general rule that a party will be deemed to have waived objection to possible inconsistencies in the jury verdict if it failed to raise such objection before the jury was discharged); Matthews v. Ohio Barge Line, Inc., 742 F.2d 202, 206 (5th Cir.1984) (failure to object to absence of separate interrogatories at trial precludes raising the issue on appeal). Although in egregious circumstances acquiescence in erroneous instructions may not be immune from remedy, see Fruge v. Penrod Drilling Co., 918 F.2d 1163, 1169 (5th Cir.1990) ("Plain error requires that plaintiff establish the challenged instruction was an incorrect statement of the law and was probably responsible for an incorrect verdict, leading

« up substantial injustice."); American Hoist & Derrick Co. v. Sowa & Sons, Inc., 725 F.2d 1350, 1364, 220 USPQ 763, 774 (Fed.Cir.1984), in this case the instructions were not in error. Thus there is no basis for BP's objection now raised.

55 BP also argues that the issue of equivalency should not have been given to the jury because Celanese did not present sufficient evidence of equivalency. Celanese states that this purported insufficiency of the evidence was not raised at trial, either by motion for directed verdict or by request for jury instruction or in any other way before the case went to the jury. A party may not challenge a verdict in a post-trial motion for judgment as a matter of law absent a properly made motion for a directed verdict at the close of all the evidence. Fed.R.Civ.P. 50(b); Hinojosa v. City of Terrell, Tex., 834 F.2d 1223, 1227-28 (5th Cir.1988) ("[A] party may only base a motion for judgment notwithstanding the verdict on a ground that he included in a prior motion for directed verdict at the close of all the evidence.") (collecting cases); Delta-X Corp. v. Baker Hughes Prod. Tools, Inc., 984 F.2d 410, 412, 25 USPQ2d 1447, 1449 (Fed.Cir.1993) (interpreting Fifth Circuit law).

56 BP's directed verdict motion did not address the issue of equivalency or the sufficiency of the evidence to show equivalency, BP arguing only that there was no infringement of the "stable" limitation based on the "dimension" definition. BP argued in its motion for judgment as a matter of law that Celanese's electron micrographic evidence, showing a macroreticulated structure for both Amberlyst TM 15 (used by Celanese) and Purolite TM (used by BP) resin, was not sufficient to prove similarity of the "way" the resin worked. Celanese states that BP's silence or inadequate objection, in its directed verdict motion, to the now-asserted deficiency in Celanese's proofs, deprived Celanese of the opportunity to cure any such deficiency before the case was submitted to the jury.

57 Providing the opportunity to the nonmovant to repair gaps in its proofs is the reason Rule 50(b) is rigorously applied. See generally Cone v. West Virginia Pulp & Paper Co., 330 U.S. 212, 67 S.Ct. 752, 91 L.Ed. 849 (1947) (discussing the opportunities pursuant to Rule 50(b) for litigants and trial judge to correct errors before appeal is taken). BP disputes Celanese's view of the content of BP's motions, stating that it moved and filed a supporting memorandum for directed verdict after plaintiff's case and at the close of the evidence, pointing out the inadequacies of the evidence. Our review of BP's memorandum in support of its motion for directed verdict detects no mention of the doctrine of equivalents; the memorandum focuses entirely on the meaning of "stable."

58 As we have discussed, on the correct claim interpretation the claims are literally infringed. This jury's verdict of infringement is consistent with our ruling based on claim interpretation. In addition, the district court reviewed the evidence, referred to the insubstantial nature of BP's variation of the patented process, and stated that the verdict of infringement was "overwhelmingly supported by the evidence." On review of the entirety of the proceeding, we have not been shown grounds for reversal or for a new trial. See Shatterproof Glass Corp. v. Libbey-Owens Ford Co., 758 F.2d 613, 225 USPQ 634 (Fed.Cir.), cert. dismissed, 474 U.S. 976, 106 S.Ct. 340, 88 L.Ed.2d 326 (1985).

E. BP's Separate Patent on its Process

59 BP directs our attention to its "Jones patent," U.S. Patent No. 5,003,104, and asks that we take judicial notice that BP is practicing a process that is separately

« up atentable, arguing that this is presumptive evidence of non-infringement.

60 BP's Jones patent was not introduced at trial, Celanese says intentionally because it showed that the Purolite TM resin used by BP was "likely macroreticulated," an issue that was contested at trial although not on appeal. As the district court remarked, a reasonable jury could have discredited the BP tests wherein the pores of the resin were first collapsed by high heat or a drying process, evidence that the district court called "extremely dubious." Although there is much argument on this point on appeal, we decline to consider disputed evidence that could have been but was not offered at trial. Indeed, the proposition for which it is offered is incorrect. See Atlas Powder Co. v. E.I. du Pont De Nemours & Co., 750 F.2d 1569, 1580, 224 USPQ 409, 417 (Fed.Cir.1984) (an improvement in a step of a patented method, even if separately patentable, may not avoid infringement). See also National Presto Indus., Inc. v. West Bend Co., 76 F.3d 1185, 1192, 37 USPQ2d 1685, 1689 (Fed.Cir.1996) (the fact of separate patentability is relevant and should be weighed, but is not dispositive of noninfringement).

61 The fact of separate patentability presents no legal or evidentiary presumption of noninfringement and, in this case, does not outweigh the substantial evidence supporting the jury verdict of infringement.Conclusion

62 On the correct interpretation of "stable" as measured by linear dimension, the claims read on the accused method. Alternatively, there was substantial evidence whereby a reasonable jury could have found infringement. The judgment of infringement is affirmed.

II

WILLFUL INFRINGEMENT

63 BP argues that the jury verdict of willful infringement should be reversed, asserting that the question of infringement was a close one, and thus can not be deemed willful as a matter of law.

64 The issue of willfulness of wrongdoing is a question of fact, and was presented to the jury for decision. On appellate review of the jury verdict, if there was substantial evidence in support of the verdict it is not subject to reversal on appeal. See Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 806 F.2d 1565, 1581, 1 USPQ2d 1081, 1091 (Fed.Cir.1986).

65 The issue of "willful" infringement measures the infringing behavior, in the circumstances in which the infringer acted, against an objective standard of reasonable commercial behavior in the same circumstances. Willful infringement is thus a measure of reasonable commercial behavior in the context of the tort of patent infringement. The extent to which the infringer disregarded the property rights of the patentee, the deliberateness of the tortious acts, or other manifestations of unethical or injurious commercial conduct, may provide grounds for a finding of willful infringement and the enhancement of damages. Amsted Indus. Inc. v. Buckeye Steel Castings Co., 24 F.3d 178, 181, 30 USPQ2d 1462, 1464 (Fed.Cir.1994). See American Medical Sys., Inc. v. Medical Eng. Corp., 6 F.3d 1523, 1531, 28 USPQ2d 1321, 1326 (Fed.Cir.1993) (determining whether infringer had a "reasonable good faith belief" in noninfringement); State Indus., Inc. v. Mor-Flo Indus., Inc., 883 F.2d 1573, 1581, 12 USPQ2d 1026, 1032 (Fed.Cir.1989) ("copying is

« up vidence of willful infringement"), cert. denied, 493 U.S. 1022, 110 S.Ct. 725, 107 ...Ed.2d 744 (1990).

The jury was instructed as follows:

66 Willful infringement is established where Celanese has proven that BP and Sterling (i) were aware of Celanese's patent; and (ii) had no reasonable basis for reaching a good faith conclusion that using their method avoided infringement of the patent. Infringement is not willful and deliberate if the party found to be infringing had a reasonable basis to believe that the patent is invalid or not infringed.

67 You may find that BP and Sterling willfully infringed the '806 patent if you find, by clear and convincing evidence, that BP and Sterling failed to exercise due care to determine whether or not they were infringing the patent, after they had actual notice of the patent.

68 BP does not assert error in the instruction, and we discern none. However, BP argues that the verdict is not supported by substantial evidence, pointing to its own evidence and the comments by the trial judge that the case was a close one. See Sun Studs, Inc. v. ATA Equipment Leasing, Inc., 872 F.2d 978, 10 USPQ2d 1338 (Fed.Cir.1989) (reviewing to determine whether jury verdict is supported by substantial evidence on the record as a whole), overruled as to laches, A.C. Aukerman Co. v. R.L. Chaides Const. Co., 960 F.2d 1020, 1038, 22 USPQ2d 1321, 1333 (Fed.Cir.1992) (en banc).

69 There was evidence that BP conducted research in an effort to avoid the Celanese process, and that BP turned to the process that was found to be infringing only after failing to find some other solution to the problem of iodide contamination. BP argues that infringement that is not literal, but is found only by equivalency, can not be willful for it shows BP's good faith effort to avoid the patent. Such facts when present are of course relevant, but it is not a rule of law that infringement that is not literal can never be sufficiently culpable to warrant enhanced damages. Although avoidance of literal infringement is a fact to be considered and weighed, along with other relevant facts, it is not an automatic exculpation. And in this case, as we have discussed, the infringement is literal.

70 BP requested reexamination of the Celanese patent six months before trial. The district court declined to stay the trial, and the proceedings went forward concurrently. This procedure was fully within the court's discretion, lest the trial schedule be manipulated or unduly delayed. However, BP also argues that the acceptance by the patent examiner of the reexamination request was evidence of the closeness of the question and supports the position that infringement was not willful.

71 We take notice that the grant by the examiner of a request for reexamination is not probative of unpatentability. The grant of a request for reexamination, although surely evidence that the criterion for reexamination has been met (i.e., that a "substantial new question of patentability" has been raised, 35 U.S.C. § 303), does not establish a likelihood of patent invalidity.[2] See Acoustical Design, Inc. v. Control Elecs. Co., 932 F.2d 939, 942, 18 USPQ2d 1707, 1710 (Fed.Cir.) ("initial rejection by the Patent and Trademark Office of original claims that later were confirmed on reexamination hardly justifies a good faith belief in the invalidity of the claims"), cert. denied, 502 U.S. 863, 112 S.Ct. 185, 116 L.Ed.2d 146 (1991).

« up The issue of willful infringement was thoroughly argued to the jury, whose determination must be upheld if any set of facts supported by substantial evidence is capable of sustaining the verdict. Orthokinetics, 806 F.2d at 1580, 1 USPQ2d at 1091. Although we do not know whether the jury's finding of infringement was based on literal infringement or on equivalency, on the entirety of the record there was substantial evidence whereby a reasonable jury could have found willfulness. The verdict must be sustained.

III

SANCTIONS

73 Celanese asserts that BP's appeal is frivolous, and requests the imposition of sanctions.

74 BP's appeal was taken as of right, on disputed and technologically complex facts. Although a jury verdict warrants deference on appeal, in light of this court's conflicting holdings, now resolved in Markman, that issues of claim interpretation in infringement actions must be decided de novo on appeal, a losing party having a colorable argument can not be faulted for seeking appellate attention after a jury trial. Although we have affirmed the district court's judgment, BP's arguments on the merits are clearly not frivolous. Unwarranted accusations of frivolousness, and the satellite litigation generated by unsupported requests for sanctions, are no less burdensome to the court and the parties than are authentically frivolous appeals.

Costs

75 No costs.

76 AFFIRMED.

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[1] Hoechst Celanese Corp. v. BP Chemicals, Ltd., 846 F.Supp. 542, 31 USPQ2d 1825 (S.D.Tex.1994)

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[2] The Annual Report of the Patent and Trademark Office for 1994 states that 89% of the reexamination requests were granted that year, but only 5.6% of the reexamined patents were completely rejected with no claims remaining after reexamination

2107.03 Special Considerations for Asserted Therapeutic or Pharmacological Utilities - 2100 Patentability

2107.03 Special Considerations for Asserted Therapeutic or Pharmacological Utilities

The Federal courts have consistently reversed rejections by the Office asserting a lack of utility for inventions claiming a pharmacological or therapeutic utility where an applicant has provided evidence that reasonably supports such a utility. In view of this, Office personnel should be particularly careful in their review of evidence provided in support of an asserted therapeutic or pharmacological utility.

I. A REASONABLE CORRELATION BETWEEN THE EVIDENCE AND THE ASSERTED UTILITY IS SUFFICIENT

As a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility. *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *Nelson v. Bowler*, 626 F.2d 853, 206 USPQ 881 (CCPA 1980). An applicant can establish this reasonable correlation by relying on statistically relevant data documenting the activity of a compound or composition, arguments or reasoning, documentary evidence (e.g., articles in scientific journals), or any combination thereof. The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use. *Nelson v. Bowler*, 626 F.2d 853, 857, 206 USPQ 881, 884 (CCPA 1980).

II. STRUCTURAL SIMILARITY TO COMPOUNDS WITH ESTABLISHED UTILITY

Courts have routinely found evidence of structural similarity to a compound known to have a particular therapeutic or pharmacological utility as being supportive of an assertion of therapeutic utility for a new compound. In *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980), the claimed compounds were found to have utility based on a finding of a close structural relationship to daunorubicin and doxorubicin and shared pharmacological activity with those compounds, both of which were known to be useful in cancer chemotherapy. The evidence of close structural similarity with the known compounds was presented in conjunction with evidence demonstrating substantial activity of the claimed compounds in animals customarily employed for screening

anticancer agents. Such evidence should be given appropriate weight in determining whether one skilled in the art would find the asserted utility credible. Office personnel should evaluate not only the existence of the structural relationship, but also the reasoning used by the applicant or a declarant to explain why that structural similarity is believed to be relevant to the applicant"s assertion of utility.

III. DATA FROM *IN VITRO* OR ANIMAL TESTING IS GENERALLY SUFFICIENT TO SUPPORT THERAPEUTIC UTILITY

If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process. A cursory review of cases involving therapeutic inventions where 35 U.S.C. 101 was the dispositive issue illustrates the fact that the Federal courts are not particularly receptive to rejections under 35 U.S.C. 101 based on inoperability. Most striking is the fact that in those cases where an applicant supplied a reasonable evidentiary showing supporting an asserted therapeutic utility, almost uniformly the 35 U.S.C. 101-based rejection was reversed. See, e.g., *In re Brana*, 51 F.3d 1560, 34 USPQ 1436 (Fed. Cir. 1995); *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881, 883 (CCPA 1980); *In re Malachowski*, 530 F.2d 1402, 189 USPQ 432 (CCPA 1976); *In re Gaubert*, 530 F.2d 1402, 189 USPQ 432 (CCPA 1975); *In re Gazave*, 379 F.2d 973, 154 USPQ 92 (CCPA 1967); *In re Hartop*, 311 F.2d 249, 135 USPQ 419 (CCPA 1962); *In re Krimmel*, 292 F.2d 948, 130 USPQ 215 (CCPA 1961). Only in those cases where the applicant was unable to come forward with any relevant evidence to rebut a finding by the Office that the claimed invention was inoperative was a 35 U.S.C. 101 rejection affirmed by the court. *In re Citron*, 325 F.2d 248, 253, 139 USPQ 516, 520 (CCPA 1963) (therapeutic utility for an uncharacterized biological extract not supported or scientifically credible); *In re Buting*, 418 F.2d 540, 543, 163 USPQ 689, 690 (CCPA 1969) (record did not establish a credible basis for the assertion that the single class of compounds in question would be useful in treating disparate types of cancers); *In re Novak*, 306 F.2d 924, 134 USPQ 335 (CCPA 1962) (claimed compounds did not have capacity to effect physiological activity upon which utility claim based). Contrast, however, *In re Buting* to *In re Gardner*, 475 F.2d 1389, 177 USPQ 396 (CCPA 1973), *reh"g denied*, 480 F.2d 879 (CCPA 1973), in which the court held that utility for a genus was found to be supported through a showing of utility for one species. In no case has a Federal court required an applicant to support an asserted utility with data from human clinical trials.

If an applicant provides data, whether from *in vitro* assays or animal tests or both, to support an asserted utility, and an explanation of why that data supports the asserted utility, the Office will determine if the data and the explanation would be viewed by one skilled in the art as being reasonably predictive of the asserted utility. See, e.g., *Ex parte Maas*, 9 USPQ2d 1746 (Bd. Pat. App. & Inter. 1987); *Ex parte Balzarini*, 21 USPQ2d 1892 (Bd. Pat. App. & Inter. 1991). Office personnel must be careful to evaluate all factors that might influence the conclusions of a person of ordinary skill in the art as to

this question, including the test parameters, choice of animal, relationship of the activity to the particular disorder to be treated, characteristics of the compound or composition, relative significance of the data provided and, most importantly, the explanation offered by the applicant as to why the information provided is believed to support the asserted utility. If the data supplied is consistent with the asserted utility, the Office cannot maintain a rejection under 35 U.S.C. 101.

Evidence does not have to be in the form of data from an art-recognized animal model for the particular disease or disease condition to which the asserted utility relates. Data from any test that the applicant reasonably correlates to the asserted utility should be evaluated substantively. Thus, an applicant may provide data generated using a particular animal model with an appropriate explanation as to why that data supports the asserted utility. The absence of a certification that the test in question is an industry-accepted model is not dispositive of whether data from an animal model is in fact relevant to the asserted utility. Thus, if one skilled in the art would accept the animal tests as being reasonably predictive of utility in humans, evidence from those tests should be considered sufficient to support the credibility of the asserted utility. *In re Hartop*, 311 F.2d 249, 135 USPQ 419 (CCPA 1962); *In re Krimmel*, 292 F.2d 948, 953, 130 USPQ 215, 219 (CCPA 1961); *Ex parte Krepelka*, 231 USPQ 746 (Bd. Pat. App. & Inter. 1986). Office personnel should be careful not to find evidence unpersuasive simply because no animal model for the human disease condition had been established prior to the filing of the application. See *In re Chilowsky*, 229 F.2d 457, 461, 108 USPQ 321, 325 (CCPA 1956) ("The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it."); *In re Wooddy*, 331 F.2d 636, 639, 141 USPQ 518, 520 (CCPA 1964) ("It appears that no one on earth is certain as of the present whether the process claimed will operate in the manner claimed. Yet absolute certainty is not required by the law. The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it.").

IV. HUMAN CLINICAL DATA

Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials. There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders (see *In re Isaacs*, 347 F.2d 889, 146 USPQ 193 (CCPA 1963); *In re Langer*, 503 F.2d 1380, 183 USPQ 288 (CCPA 1974)), even with respect to situations where no art-recognized animal models existed for the human disease encompassed by the claims. *Ex parte Balzarini*, 21 USPQ2d 1892 (Bd. Pat. App. & Inter. 1991) (human clinical data is not required to demonstrate the utility of the claimed invention, even though those skilled in the art might not accept other evidence to establish the efficacy of the claimed therapeutic compositions and the operativeness of the claimed methods of treating humans). Before a drug can enter human clinical trials, the sponsor, often the applicant, must provide a convincing rationale to those especially skilled in the art (e.g., the Food and Drug Administration) that the investigation may be successful. Such a rationale would provide a basis for the sponsor's expectation that the

investigation may be successful. In order to determine a protocol for phase I testing, the first phase of clinical investigation, some credible rationale of how the drug might be effective or could be effective would be necessary. Thus, as a general rule, if an applicant has initiated human clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.

V. SAFETY AND EFFICACY CONSIDERA-TIONS

The Office must confine its review of patent applications to the statutory requirements of the patent law. Other agencies of the government have been assigned the responsibility of ensuring conformance to standards established by statute for the advertisement, use, sale or distribution of drugs. The FDA pursues a two-prong test to provide approval for testing. Under that test, a sponsor must show that the investigation does not pose an unreasonable and significant risk of illness or injury and that there is an acceptable rationale for the study. As a review matter, there must be a rationale for believing that the compound could be effective. If the use reviewed by the FDA is not set forth in the specification, FDA review may not satisfy 35 U.S.C. 101. However, if the reviewed use is one set forth in the specification, Office personnel must be extremely hesitant to challenge utility. In such a situation, experts at the FDA have assessed the rationale for the drug or research study upon which an asserted utility is based and found it satisfactory. Thus, in challenging utility, Office personnel must be able to carry their burden that there is no sound rationale for the asserted utility even though experts designated by Congress to decide the issue have come to an opposite conclusion. "FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws." *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995) (citing *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994)).

Thus, while an applicant may on occasion need to provide evidence to show that an invention will work as claimed, it is improper for Office personnel to request evidence of safety in the treatment of humans, or regarding the degree of effectiveness. See *In re Sichert*, 566 F.2d 1154, 196 USPQ 209 (CCPA 1977); *In re Hartop*, 311 F.2d 249, 135 USPQ 419 (CCPA 1962); *In re Anthony*, 414 F.2d 1383, 162 USPQ 594 (CCPA 1969); *In re Watson*, 517 F.2d 465, 186 USPQ 11 (CCPA 1975); *In re Krimmel*, 292 F.2d 948, 130 USPQ 215 (CCPA 1961); *Ex parte Jovanovics*, 211 USPQ 907 (Bd. Pat. App. & Inter. 1981).

VI. TREATMENT OF SPECIFIC DISEASE CONDITIONS

Claims directed to a method of treating or curing a disease for which there have been no previously successful treatments or cures warrant careful review for compliance with 35 U.S.C. 101. The credibility of an asserted utility for treating a human disorder may be more difficult to establish where current scientific understanding suggests that such a task would be impossible. Such a determination has always required a good understanding of the state of the art as of the time that the invention was made. For example, prior to the

1980's, there were a number of cases where an asserted use in treating cancer in humans was viewed as "incredible." *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Buting*, 418 F.2d 540, 163 USPQ 689 (CCPA 1969); *Ex parte Stevens*, 16 USPQ2d 1379 (Bd. Pat. App. & Inter. 1990); *Ex parte Busse*, 1 USPQ2d 1908 (Bd. Pat. App. & Inter. 1986); *Ex parte Krepelka*, 231 USPQ 746 (Bd. Pat. App. & Inter. 1986); *Ex parte Jovanovics*, 211 USPQ 907 (Bd. Pat. App. & Inter. 1981). The fact that there is no known cure for a disease, however, cannot serve as the basis for a conclusion that such an invention lacks utility. Rather, Office personnel must determine if the asserted utility for the invention is credible based on the information disclosed in the application. Only those claims for which an asserted utility is not credible should be rejected. In such cases, the Office should carefully review what is being claimed by the applicant. An assertion that the claimed invention is useful in treating a symptom of an incurable disease may be considered credible by a person of ordinary skill in the art on the basis of a fairly modest amount of evidence or support. In contrast, an assertion that the claimed invention will be useful in "curing" the disease may require a significantly greater amount of evidentiary support to be considered credible by a person of ordinary skill in the art. *In re Sichert*, 566 F.2d 1154, 196 USPQ 209 (CCPA 1977); *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980). See also *Ex parte Ferguson*, 117 USPQ 229 (Bd. Pat. App. & Inter. 1957).

In these cases, it is important to note that the Food and Drug Administration has promulgated regulations that enable a party to conduct clinical trials for drugs used to treat life threatening and severely-debilitating illnesses, even where no alternative therapy exists. See 21 CFR 312.80-88 (1994). Implicit in these regulations is the recognition that experts qualified to evaluate the effectiveness of therapeutics can and often do find a sufficient basis to conduct clinical trials of drugs for incurable or previously untreatable illnesses. Thus, affidavit evidence from experts in the art indicating that there is a reasonable expectation of success, supported by sound reasoning, usually should be sufficient to establish that such a utility is credible.

904.01 Analysis of Claims - 900 Prior Art, Classification, and Search

904.01 Analysis of Claims

The breadth of the claims in the application should always be carefully noted; that is, the examiner should be fully aware of what the claims do *not* call for, as well as what they do require. During patent examination, the claims are given the broadest reasonable interpretation consistent with the specification. See *In re Morris*, 127 F.3d 1048, 44 USPQ2d 1023 (Fed. Cir. 1997). See MPEP § 2111 - § 2116.01 for case law pertinent to claim analysis.

2111 Claim Interpretation; Broadest Reasonable Interpretation [R-5]

CLAIMS MUST BE GIVEN THEIR BROADEST REASONABLE INTERPRETATION

During patent examination, the pending claims must be "given their broadest reasonable interpretation consistent with the specification." >The Federal Circuit's *en banc* decision in *Phillips v. AWH Corp.*, 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir. 2005) expressly recognized that the USPTO employs the "broadest reasonable interpretation" standard:

The Patent and Trademark Office ("PTO") determines the scope of claims in patent applications not solely on the basis of the claim language, but upon giving claims their broadest reasonable construction "in light of the specification as it would be interpreted by one of ordinary skill in the art." *In re Am. Acad. of Sci. Tech. Ctr.*, 367 F.3d 1359, 1364[, 70 USPQ2d 1827] (Fed. Cir. 2004). Indeed, the rules of the PTO require that application claims must "conform to the invention as set forth in the remainder of the specification and the terms and phrases used in the claims must find clear support or antecedent basis in the description so that the meaning of the terms in the claims may be ascertainable by reference to the description." 37 CFR 1.75(d)(1).

415 F.3d at 1316, 75 USPQ2d at 1329. See also< *In re Hyatt*, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). Applicant always has the opportunity to amend the claims during prosecution, and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. *In re Prater*, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-51 (CCPA 1969) (Claim 9 was directed to a process of analyzing data generated by mass spectrographic analysis of a gas. The process comprised selecting the data to be analyzed by subjecting the data to a mathematical manipulation. The examiner made rejections under 35 U.S.C. 101 and 102. In the 35 U.S.C. 102 rejection, the examiner explained that the claim was anticipated by a mental process augmented by pencil and paper markings. The court agreed that the claim was not limited to using a machine to carry out the process since the claim did not explicitly set forth the machine. The court explained that "reading a claim in light of the specification, to thereby interpret limitations explicitly recited in the claim, is a quite different thing from 'reading limitations of the specification into a claim,' to thereby narrow the scope of the claim by implicitly adding disclosed limitations which have no express basis in the claim." The court found that applicant was advocating the latter, i.e., the impermissible importation of subject matter from the specification into the claim.). See also *In re Morris,* 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997) (The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment

by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification.").

The broadest reasonable interpretation of the claims must also be consistent with the interpretation that those skilled in the art would reach. *In re Cortright*, 165 F.3d 1353, 1359, 49 USPQ2d 1464, 1468 (Fed. Cir. 1999) (The Board's construction of the claim limitation "restore hair growth" as requiring the hair to be returned to its original state was held to be an incorrect interpretation of the limitation. The court held that, consistent with applicant's disclosure and the disclosure of three patents from analogous arts using the same phrase to require only some increase in hair growth, one of ordinary skill would construe "restore hair growth" to mean that the claimed method increases the amount of hair grown on the scalp, but does not necessarily produce a full head of hair.).

904 How to Search [R-5]

The examiner, after having obtained a thorough understanding of the invention disclosed and claimed in the nonprovisional application, then searches the prior art as disclosed in patents and other published documents, i.e., nonpatent literature (NPL). Any document used in the rejection of a claim is called a reference. An inventor name search should be made to identify other applications and/or patents which may be applicable as references for double patenting rejections. See MPEP § 804.

In all continuing applications, the parent applications should be reviewed by the examiner for pertinent prior art. Where the cited prior art of a parent application has been reviewed, this fact should be made of record in accordance with the procedure set forth at paragraph II.(E) of MPEP § 719.05. For national stage applications filed under 35 U.S.C. 371, the examiner will consider the documents cited in an international search report when the Form PCT/DO/EO/903 indicates that both the international search report and the copies of the documents are present in the national stage application file. See MPEP § 609.03.

The first search should be such that the examiner need not ordinarily make a second search of the prior art, unless necessitated by amendments to the claims by the applicant in the first reply, except to check to determine whether any reference which would appear to be substantially more pertinent than the prior art cited in the first Office action has become available subsequent to the initial prior art search. The first search should cover the invention as described and claimed, including the inventive concepts toward which the claims appear to be directed. It should not be extended merely to add immaterial variants.

In the first action on the merits of an application, the examiner must complete the Image File Wrapper (IFW) search notes form in *>the Office Action Correspondence Subsystem (OACS)< to include the classes and subclasses of domestic and foreign patents, abstract collections, and publications in which the search for prior art was made. Other information collections and sources in which the search for prior art was made must also be identified by the examiner. The examiner must also indicate the date(s) on which the search was conducted. Note MPEP § 719.05.

In subsequent actions, where the search is brought **>up-to-date< and/or where a further search is made, the examiner must indicate on the IFW search notes form that the search has been updated and/or identify the additional field of search. See MPEP § 719.05. Any search updates should include all of the relevant or pertinent databases and the search queries and classifications employed in the original search.